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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/165, C07D 235/56 | A1

(11) International Publication Number: WO 00/06146

(43) International Publication Date: 10 February 2000 (10.02.00)

(21) International Application Number: PCT/US99/17121

(22) International Filing Date: 28 July 1999 (28.07.99)

(30) Priority Data:

| | | |
|---|---|---|
| 60/094,406 | 28 July 1998 (28.07.98) | US |
| 60/134,157 | 14 May 1999 (14.05.99) | US |

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(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published**

*With international search report.*

*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: SUBSTITUTED ANILIDE COMPOUNDS AND METHODS

(57) Abstract

This invention relates to substituted anilide compounds which are modulators, agonists or antagonists, of the CCR5 receptor. In addition, this invention relates to the treatment and prevention of disease states mediated by CCR5.

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# SUBSTITUTED ANILIDE COMPOUNDS AND METHODS

## FIELD OF THE INVENTION

This invention relates to substituted anilide compounds which are modulators, agonists or antagonists, of the CC chemokine receptor CC-CKR5 now designated as CCR5 (*Nature Medicine* **1996**, *2*, 1174-8). In addition, this invention relates to the treatment and prevention of disease states mediated by CCR5.

## BACKGROUND OF THE INVENTION

T cells are not only key regulators of the immune response to infectious agents but are believed critical for the initiation and maintenance of the inflammatory reaction in a variety of chronic diseases. Increased numbers or enhanced activation state of T cells, especially CD4+ T cells, have been demonstrated in the synovium of individuals with rheumatoid arthritis (M.J. Elliott and R. N. Maini, Int. Arch. Allergy Immunol. 104: 112-1125, 1994), in the bronchial mucosa of asthmatics (C.J. Corrigan and A.B. Kay, Immunol. Today 13:501-506, 1992), in the lesions of multiple sclerosis (R. Martin and H. F. McFarland, Crit. Rev. Clin. Lab. Sci. 32: 121-182, 1995), in psoriatic lesions (J.L. Jones, J. Berth-Jone, A. Fletcher and P.E. Hutchinson, J. Pathol. 174: 77-82, 1994) and in the fatty streaks of atherosclerosis (R. Ross, Annu. Rev. Physiol. 57: 791-804, 1995).

T cells, as well as other inflammatory cells, will migrate into tissues in response to the production of a variety of chemotactic factors. Among these factors are a superfamily of 8-12 kDa proteins known as the chemokines. These proteins share structural features such as the presence of 3-4 conserved cysteine residues. RANTES, which stands for Regulated upon Activation Normal T cell Expressed and Secreted, is an 8 kDa protein member of CC branch of the chemokine family. These proteins recruit and activate immune and inflammatory cells through an interaction with G-protein coupled receptors. The CC branch is defined by the absence of an intervening amino acid residue between the first two cysteine residues and members of this family predominately elicit the migration of mononuclear cells, eosinophils and basophils (M. Baggiolini, B. Dewald, and B. Moser, Adv. Immunol. 55: 97-179, 1994; and J.J. Oppenheim, C.O.C. Zachariae, N. Mukaida, and K. Matsushima, Annu. Rev. Immunol. 9: 617-648, 1991).

RANTES potently produces chemotaxis of T cells, basophils, eosinophils, monocytes and mast cells. RANTES was originally identified as gene product induced late after antigen activation of T-cells (T.J. Schall, J. Jongstra, B.J. Dyer, J. Jorgensen, et al., J. Immunol. 141:1018-1025, 1988), however, RANTES has been shown to be synthesized and secreted by a diverse group of cells that include

epithelial and endothelial cells (C. Stellato, L.A. Beck, G.A. Gorgone, D. Proud, et al., J. Immunol. 155: 410-418, 1995; and A. Marfaing-Koka, O. Devergne, G. Gorgone, A. Portier, et al., J. Immunol. 154: 1870-1878, 1994), synovial fibroblasts (P. Rathanaswami, M. Hachicha, M. Sadick, T.J. Schall, et al., J. Biol. Chem. 268: 5834-5839, 1993) and dermal fibroblasts (M. Sticherling, M. Kupper, F. Koltrowitz, E. Bornscheuer, et al., J. Invest. Dermatol. 105: 585-591, 1995), mesangial cells (G. Wolf, S. Aberle, F. Thaiss, et al., Kidney Int. 44: 795-804, 1994) and platelets (Y. Koameyoshi, A. Dorschner, A.I. Mallet, E. Christophers, et al., J. Exp. Med. 176: 587-592, 1992). In these cells RANTES mRNA is rapidly upregulated in response to IL-1 or TNF•. Although RANTES mRNA is not usually detected in normal tissues (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995), increased mRNA or protein has been found in diseases characterized by a mononuclear infiltrate. For example, RANTES mRNA was visualized using *in situ* hybridization in renal allografts undergoing rejection (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995; and K.C. Nadeau, H. Azuma and N.I. Tilney, Proc. Natl. Acad. USA 92: 8729-8733, 1995) in the skin of atopic dermatitis patients after exposure to antigen (S. Ying, L. Taborda-Barata, Q. Meng, M. Humbert, et al., J. Exp. Med. 181: 2153-2159, 1995), and in endothelial cells of coronary arteries undergoing accelerated atherosclerosis after cardiac transplant (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995). Further, increased immunoreactive protein for RANTES has been detected in bronchoalveolar lavage fluid (R. Alam, J. York, M. Boyers, et al., Am. J. Resp. Crit. Care Med. 149: A951, 1994) and sputum from asthmatic individuals (C.M. Gelder, P.S. Thomas, D.H. Yates, I.M. Adcock, et al., Thorax 50: 1033-1037, 1995).

Several receptors have been identified that bind RANTES. In particular, CCR5, when expressed in either HEK 293 cells or CHO cells, binds RANTES. This receptor is expressed in T-cells and in monocytes and macrophages, immune/inflammatory cells which are important in the maintenance of a chronic inflammatory reaction. Pharmacological characterization of CCR5 indicates similarities to the RANTES binding site observed on isolated T cells. Therefore, antagonism of RANTES' action on CCR5, as well as antagonism of other natural modulators of CCR5, should inhibit the recruitment and activation of T cells and macrophages into inflammatory lesions and provide a novel therapeutic approach for the treatment of atopic and autoimmune disorders.

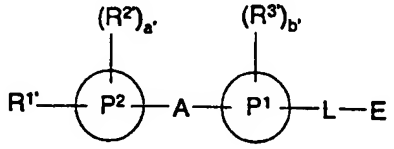
Since T cells and macrophages express CCR5, selective receptor modulators of CCR5, particularly antagonists, are likely to provide beneficial effects in diseases including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases,

atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease, all in mammals, preferably humans. Furthermore, since CD8+ T cells and macrophages have been implicated in COPD, CCR5 may play a role in their recruitment and therefore antagonists to CCR5 could provide potential therapeutic in the treatment of COPD. Also, since CCR5 is a co-receptor for the entry of HIV into cells, selective receptor modulators may be useful in the treatment of HIV infection.

Surprisingly, it has now been discovered that this class of non-peptide compounds, in particular substituted anilide compounds of this invention, function as CCR5 receptor modulators, and therefore, have utility in the treatment and prevention of disease states mediated by CCR5 receptor mechanisms.

## SUMMARY OF THE INVENTION

In one aspect, the present invention is to novel compounds of formula (I), or pharmaceutically active salts thereof, and their novel use in treating the above-mentioned CCR5-mediated disease states:




Formula I

wherein:

the basic nitrogen in moiety E may be optionally quaternized with $C_{1-6}$alkyl or is optionally present as the N-oxide;

$P^1$ and $P^2$ are independently phenyl, fused bicyclic aryl, a monocyclic heterocyclic ring of 5- to 7-members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, or a fused bicyclic heterocyclic ring of 8 to 11-members containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

A is $C(R^{4'})_2$, $CR^{4'}(OR^{5'})$, CO, $C{=}NOR^{6'}$, $NR^{7'}$, oxygen, or $S(O)_{c'}$;

L is a group of formula $-C(=V)-DR^{8'}-$, $-DR^{9'}-C(=V)-$, $-CH_2NH-$, or $-NHCH_2-$;

V is oxygen or sulfur;

D is nitrogen, carbon, or a CH group,

$R^{1'}$ and $R^{2'}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkenyl, aryl, $(CH_2)_{d'}NR^{10'}R^{11'}$, $(CH_2)_{d'}NR^{10'}COR^{12'}$, $(CH_2)_{d'}NR^{10'}CO_2R^{13'}$, $(CH_2)_{d'}NR^{10'}SO_2R^{14'}$,

$(CH_2)_dCONR^{15'}R^{16'}$, hydroxy$C_{1-6}$alkyl, $C_{1-4}$alkoxyalkyl (optionally substituted by a $C_{1-4}$alkoxy or hydroxy group), $(CH_2)_dCO_2C_{1-6}$alkyl, $(CH_2)_eOC(O)R^{17'}$, $CR^{18'}=NOR^{19'}$, $CNR^{20'}=NOR^{19'}$, $COR^{21'}$, $CONR^{15'}R^{16'}$, $CONR^{15'}(CH_2)_fOC_{1-4}$alkyl, $CONR^{15'}(CH_2)_dCO_2R^{22'}$, $CONHNR^{23'}R^{24'}$, $CONR^{15'}SO_2R^{25'}$, $CO_2R^{26'}$, cyano, trifluoromethyl, $NR^{10'}R^{11'}$, $NR^{10'}COR^{12'}$, $NR^{27'}CO(CH_2)_dNR^{27'}R^{28'}$, $NR^{27'}CONR^{27'}R^{28'}$, $NR^{10'}CO_2R^{13'}$, $NR^{10'}SO_2R^{14'}$, $N=CNR^{27'}NR^{27'}R^{28'}$, nitro, hydroxy, $C_{1-6}$alkoxy, hydroxy$C_{1-6}$alkoxy, $C_{1-6}$alkoxy$C_{1-6}$alkoxy, $OC(O)NR^{29'}R^{30'}$, $SR^{31'}$, $SOR^{32'}$, $SO_2R^{32'}$, $SO_2NR^{33'}R^{34'}$, halogen, $C_{1-6}$alkanoyl, $CO_2(CH_2)_dOR^{35'}$, or $R^{1'}$ is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;

$R^{3'}$ is hydrogen, $C_{1-6}$alkyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkenyl, hydroxy$C_{1-6}$alkyl, $C_{1-6}$alkyl$OC_{1-6}$alkyl, $CONR^{36'}R^{37'}$, $CO_2R^{38'}$, cyano, aryl, trifluoromethyl, $NR^{39'}R^{40'}$, nitro, hydroxy, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, acyloxy, or halogen;

$R^{4'}$, $R^{5'}$, $R^{6'}$, $R^{7'}$, $R^{18'}$, $R^{19'}$, $R^{20'}$, $R^{21'}$, $R^{22'}$, $R^{23'}$, $R^{24'}$, $R^{27'}$, $R^{28'}$, $R^{31'}$, $R^{35'}$, $R^{36'}$, $R^{37'}$, $R^{38'}$, $R^{39'}$, and $R^{40'}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{8'}$ is hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group;

$R^{9'}$ is hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group;

$R^{10'}$ and $R^{11'}$ are independently hydrogen or $C_{1-6}$alkyl, or $R^{10'}$ and $R^{11'}$ together with the nitrogen to which they are attached, forms a 5- to 6-membered heterocyclic ring, which may optionally be substituted by an oxo group, and, when there are six members, may optionally contain in the ring one oxygen or one sulfur atom;

$R^{12'}$ is hydrogen, $C_{1-6}$alkyl, or $C_{1-4}$alkoxyalkyl;

$R^{13'}$, $R^{25'}$, and $R^{32'}$ are independently $C_{1-6}$alkyl;

$R^{14'}$ is $C_{1-6}$alkyl or phenyl;

$R^{15'}$ and $R^{16'}$ are independently hydrogen or $C_{1-6}$alkyl, or $R^{15'}$ and $R^{16'}$ together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when there are 6 ring members, may optionally contain in the ring one oxygen or one sulfur atom;

$R^{17'}$ is $C^{1-4}$alkyl, optionally substituted by $C_{1-6}$alkoxy;

$R^{26'}$ is hydrogen or $C_{1-6}$alkyl optionally substituted with one or two substituents selected from $C_{1-6}$alkyl, $C_{1-6}$alkoxy, hydroxy, or $NR^{10'}R^{11'}$;

$R^{29'}$ and $R^{30'}$ are independently hydrogen or $C_{1-6}$alkyl, or $R^{29'}$ and $R^{30'}$ together with the nitrogen to which they are attached form a 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or sulfur atom;

$R^{33'}$ and $R^{34'}$ are independently hydrogen or $C_{1-6}$alkyl, or $R^{33'}$ and $R^{34'}$ together with the nitrogen to which they are attached form 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or one sulfur atom;

a' and b' are independently 1, 2, or 3;

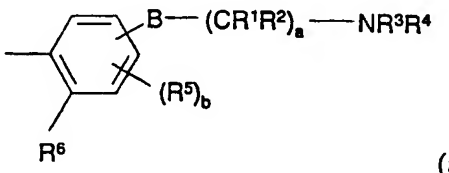
c' is 0, 1, or 2;

d' is 1, 2, 3, or 4;

e' is 0, 1, 2, or 3;

f' is 1, 2, or 3;

E represents (a):




(a);

in which

B is oxygen, $S(O)_c$, $CR^7{=}CR^8$, or $CR^7R^8$, or B is $NR^9$;

$R^1$ and $R^2$ are independently hydrogen or $C_{1-6}$alkyl; alternatively $B(CR^1R^2)_a$ is $OCR^1R^2CR^1(OH)CR^1R^2$ or $OCR^1R^2CR^1(OCOCH_3)CR^1R^2$;

$R^3$ and $R^4$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, hydroxy, $OCOR^{12}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{13}$, and $NHCO_2R^{14}$;

$R^5$ is hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{15}R^{16}$, $CO_2R^{17}$, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$ or halogen;

$R^6$ is hydrogen, $C_{1-6}$alkyl, aryl, trifluoromethyl, hydroxy, $C_{1-6}$alkoxy or halogen, or $R^6$ taken together with $R^{8'}$ forms a group D where D is $(CR^{22}R^{23})_e$ or D is $(CR^{22}R^{23})_f$-G where G is oxygen, sulfur or $CR^{22}{=}CR^{23}$, $CR^{22}{=}N$, $=CR^{22}O$, $=CR^{22}S$, or $=CR^{22}$-$NR^{23}$;

$R^7$, $R^8$, $R^{10}$, $R^{11}$, $R^{12}$, $R^{15}$, $R^{16}$, $R^{17}$, $R^{20}$, $R^{21}$, $R^{22}$, and $R^{23}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^9$ is hydrogen, $C_{1-6}$alkyl, or phenyl$C_{1-6}$alkyl;

$R^{13}$, $R^{14}$, $R^{18}$, and $R^{19}$ are independently $C_{1-6}$alkyl;

a is 1, 2, 3, or 4;

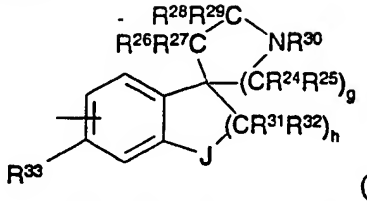
b is 1 or 2;

c and d are independently 0, 1 or 2;

e is 2, 3 or 4;

f is 0, 1, 2 or 3;

alternatively, E represents (b):



(b);

$R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{31}$, and $R^{32}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{30}$ is hydrogen, $C_{1-6}$alkyl, or $C_{3-7}$cycloalkyl;

$R^{33}$ is hydrogen, $C_{1-6}$alkyl, trifluoromethyl, hydroxy, or halogen, or $R^{33}$ and $R^{8'}$ together form a group -K- where K is $(CR^{34}R^{35})_i$ or K is $(CR^{34}R^{35})_j$ -M and M is oxygen, sulfur, $CR^{34}=CR^{35}$, $CR^{34}=N$, or N=N;

J is oxygen, $CR^{36}R^{37}$, or $NR^{38}$, or J is a group $S(O)_k$;

$R^{34}$, $R^{35}$, $R^{36}$, $R^{37}$, and $R^{38}$ are independently hydrogen or $C_{1-6}$alkyl;

g is 1, 2 or 3;

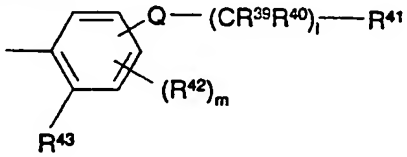
h is 1, 2 or 3;

i is 2, 3, or 4;

j is 0, 1, 2, or 3;

k is 0, 1 or 2;

alternatively, E represents (c):



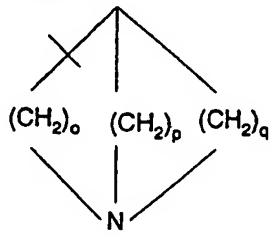
(c);

in which:

Q is oxygen, $S(O)_n$, $CR^{44}=CR^{45}$, $CR^{44}R^{45}$, or Q is $NR^{46}$;

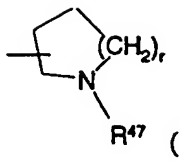
$R^{39}$ and $R^{40}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{41}$ is a group of formula (d):



(d)

or $R^{41}$ is a group of formula (e):



(e)

$R^{42}$ is hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{48}R^{49}$, $CO_2R^{50}$, trifluoromethyl, $NHCO_2R^{51}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_sR^{52}$, $SO_2NR^{53}R^{54}$, or halogen;

$R^{43}$ is hydrogen or $R^{43}$ together with $R^{8'}$ forms a group R where R is $CR^{55}=CR^{56}$, $CR^{55}=CR^{56}CR^{55}R^{56}$, or $(CR^{55}R^{56})_t$;

$R^{44}$, $R^{45}$, $R^{46}$, $R^{48}$, $R^{49}$, $R^{50}$, $R^{53}$, $R^{54}$, $R^{55}$, and $R^{56}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{47}$ is hydrogen, $C_{1-6}$alkyl, or $C_{3-7}$ cycloalkyl;

$R^{51}$ and $R^{52}$ are independently $C_{1-6}$alkyl;

l is 0, 1, 2, or 3;

m is 1 or 2;

n is 0, 1, or 2

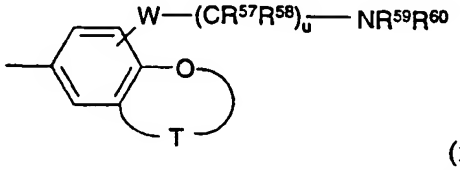
o, p, and q are independently integers having the value 1, 2, or 3;

r is 0,1, 2, or 3;

s is 0, 1, or 2;

t is 2 or 3;

alternatively, E represents (f):



(f);

$R^{57}$ and $R^{58}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{59}$ and $R^{60}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{61}R^{62}$, $NR^{61}R^{62}$, hydroxy, $OCOR^{63}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{64}$, and $NHCO_2R^{65}$;

T is $-(CR^{66}R^{67})_v-$ or $-O(CR^{66}R^{67})_w-$;

W is oxygen, $S(O)_x$, $NR^{68}$, or W is $CR^{69}=CR^{70}$ or $CR^{69}R^{70}$;

$R^{61}$, $R^{62}$, $R^{63}$, $R^{66}$, $R^{67}$ $R^{68}$, $R^{69}$, and $R^{70}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{64}$ and $R^{65}$ are independently $C_{1-6}$alkyl;

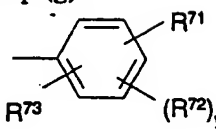
u is 1 to 4;

v is 2 or 3;

w is 1, 2, or 3;

x is 0, 1 or 2;

alternatively, E represents a group (g):



(g);

$R^{71}$ is an optionally substituted 5 to 7-membered saturated or partially saturated heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur or $R^{71}$ is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom and optionally a further heteroatom selected from oxygen, nitrogen or sulfur;

$R^{72}$ is hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{74}R^{75}$, $CO_2R^{76}$, trifluoromethyl, $NHCO_2R^{77}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_zR^{78}$, $SO_2NR^{79}R^{80}$, or halogen;

$R^{73}$ is hydrogen, $C_{1-6}$alkyl, hydroxy, $C_{1-6}$alkoxy or halogen, or $R^{73}$ and $R^{8'}$ taken together from a group -X- where X is $(CR^{81}R^{82})_{aa}$ or X is $(CR^{81}R^{82})_{ab}$-Y and Y is oxygen, sulfur or $CR^{81}=CR^{82}$;

$R^{74}$, $R^{75}$, $R^{76}$, $R^{79}$, $R^{80}$, $R^{81}$, and $R^{82}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{77}$ and $R^{78}$are independently $C_{1-6}$alkyl;

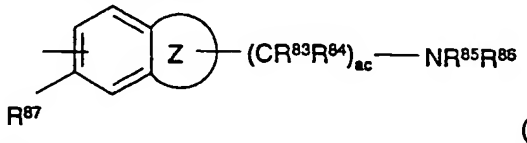
y is 1 or 2;

z is 0, 1, or 2;

aa is 2, 3 or 4;

ab is 0, 1, 2 or 3;

alternatively, E represents group (h):



(h);

$R^{83}$ and $R^{84}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{85}$ and $R^{86}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{88}R^{89}$, $NR^{90}R^{91}$, hydroxy, $OCOR^{92}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{93}$, and $NHCO_2R^{94}$;

$R^{87}$ is hydrogen or $C_{1-6}$alkyl, $C_{1-6}$alkoxy, or halogen, or $R^{87}$ together with $R^{8'}$ forms a group -AA- where AA is $(CR^{95}R^{96})_{ad}$ or AA is $(CR^{95}=CR^{96})_{ae}$-AB and AB is oxygen, sulfur, $CR^{95}=CR^{96}$, $CR^{95}=N$, $CR^{95}NR^{96}$ or N=N;

Z is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

$R^{88}$, $R^{89}$, $R^{90}$, $R^{91}$, $R^{92}$, $R^{95}$, and $R^{96}$ are independently hydrogen or $C_{1-6}$alkyl;

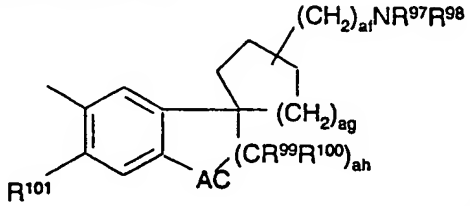
$R^{93}$ and $R^{94}$ are independently $C_{1-6}$alkyl;

ac is 0 to 4;

ad is 1, 2 or 3;

ae is 0, 1 or 2;

alternatively, E represents group (i):




(i);

$R^{97}$ and $R^{98}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{102}R^{103}$, $NR^{104}R^{105}$, hydroxy, $OCOR^{106}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{107}$, and $NHCO_2R^{108}$;

$R^{99}$ and $R^{100}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{101}$ is hydrogen or $C_{1-6}$alkyl or $R^{101}$ and $R^{8'}$ together form a group -AD- where AD is $(CR^{109}R^{110})$ai or AD is $(CR^{109}R^{110})_{aj}$-AE and AE is oxygen, sulfur or $CR^{109}=CR^{110}$;

AC is oxygen, $CR^{111}R^{112}$ or $NR^{113}$ or AC is a group $S(O)_{ak}$;

$R^{102}$, $R^{103}$, $R^{104}$, $R^{105}$, $R^{106}$, $R^{109}$, $R^{110}$, $R^{111}$, $R^{112}$, and $R^{113}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{107}$ and $R^{108}$ are independently $C_{1-6}$alkyl;

af is 0, 1, 2, 3, or 4;

ag is 1, 2, or 3;

ah is 1, 2, 3 or 4;

ai is 2, 3 or 4;

aj is 0, 1, 2, or 3; and

ak is 0, 1 or 2.

In another aspect, the present invention is to a method of treating CCR5 mediated disease states, including, but not limited to, COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic disease, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease and HIV infection, all in mammals, preferably humans, comprising administering to such mammal in need thereof, a anilide of formula (I), or pharmaceutically active salts thereof.

In yet another aspect, the present invention is to pharmaceutical compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier therefor. In particular, the pharmaceutical compositions of the present invention are used for treating CCR5-mediated disease states, including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic disease, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, COPD and HIV all in mammals, preferably humans.

## DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that substituted anilides of formula (I) are CCR5 receptor modulators. It has also now been discovered that selective inhibition of CCR5 receptor mechanisms by treatment with the receptor modulators of formula (I), or a pharmaceutically acceptable salt thereof, represents a novel therapeutic and preventative approach to the treatment of a variety of disease states, including, but not limited to, COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic disease, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease, all in mammals, preferably humans ("CCR5-mediated diseases"). Also, since CCR5 is a co-receptor for the entry of HIV into cells, selective receptor modulators may be useful in the treatment of HIV infection.

The term "alkyl" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

The terms "cycloalkyl" and "cyclic alkyl" are used herein at all occurrences to mean cyclic radicals, preferably comprising 3 to 7 carbon atoms which may be mono- or bicyclo-fused ring systems which may additionally include unsaturation, including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, and the like.

The terms "halo" or "halogen" are used interchangeably herein at all occurrences to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The term "heterocyclic ring" is used herein at all occurrences to mean a saturated or partially saturated 5-, 6-, or 7-membered ring system (unless the cyclic ring system is otherwise limited) in which the ring system contains one to 3 heteroatoms selected from oxygen, sulfur, or nitrogen, which ring system may be optionally substituted with $C_{1-6}$alkyl or $C_{3-7}$cycloalkyl. Examples of such rings include, but are not limited to, piperidine, tetrahydropyridine, and piperazine. When the heterocyclic ring is fused to a phenyl group, the term "heterocyclic ring", together with the phenyl ring to which it is fused, forms a ring which includes, but is not limited to, dihydro-1,4-benzoxazine and 1,2,3,4-tetrahydroquinoline, which may be optionally substituted by $C_{1-6}$alkyl or oxo.

The term "6,6 or 6,5 bicyclic ring" means a 6,6 or 6,5-bicyclic ring system containing a nitrogen atom and optionally a further heteroatom selected from nitrogen, oxygen, or sulfur, which ring system may be optionally substituted with $C_{1-6}$alkyl. Examples of such ring systems include, but are not limited to, tropane, isoquinuclidine and granatane rings.

The term "CCR5 mediated disease state" is used herein at all occurrences to mean any disease state which is mediated (or modulated) by CCR5.

The term "monocyclic heterocyclic ring" is used herein at all occurrences to mean a single aromatic ring of 5 to 7 members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur represented by $P^1$ and/or $P^2$ including thienyl, furyl, pyrrolyl, and pyridyl.

The term "fused bicyclic heterocyclic ring" is used herein at all occurrences to mean a fused bicyclic ring system of 8 to 11 members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur including indole, benzofuran, benzothiophene, quinoline, and isoquinoline rings.

Suitably, pharmaceutically acceptable salts of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate, or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate, and stearate.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like, are equivalent to the unsolvated forms for purposes of this invention.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. The stereocenters may be of any combination of R and S configuration, for example, (R,R), (R,S), (S,S) or (S,R). All of these compounds are within the scope of the present invention.

For the compounds of formula (I) various embodiments are as follows. It will be understood that the basic nitrogen in moiety E may be optionally quaternized with $C_{1-6}$alkyl or is optionally present as the N-oxide.

$P^1$ and $P^2$ are suitably independently phenyl, fused bicyclic aryl, a monocyclic heterocyclic ring of 5- to 7-members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, or a fused bicyclic heterocyclic ring of 8 to 11-members containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur. Preferably, $P^1$ is phenyl and $P^2$ is phenl or quinoxalinyl. More preferably $P^1$ and $P^2$ are phenyl.

When $R^{1'}$ is a 5- to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen, or sulfur, suitable heterocyclic rings include aromatic groups such as thienyl, furyl, pyrrolyl, triazolyl, diazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, and dioxanyl. Saturated and partially saturated rings are also within the scope of the invention, in particular rings including an oxo or thioxo moiety such as lactams and thiolactams. Suitably, the heterocyclic ring can be linked to the remainder of the molecule via a carbon atom, or, when present, a nitrogen atom. Suitable substituents for these rings include one to two of $R^{3'}$.

A is $C(R^{4'})_2$, $CR^{4'}(OR^{5'})$, CO, $C{=}NOR^{6'}$, $NR^{7'}$, oxygen, or $S(O)_{c'}$. Preferably A is $C(R^{4'})_2$, CO, $C{=}NOR^{6'}$, $NR^{7'}$, oxygen, or sulfur. More preferably, A is $CH_2$, CO, C=NOH, oxygen or sulfur. Most preferably, A is $CH_2$, CO, oxygen or sulfur. Preferably, A is attached to $P^1$ meta or para to L, more preferably, A is attached to $P^1$ para to L.

L is suitably a group of formula $-C(=V)-DR^{8'}-$, $-DR^{9'}-C(=V)-$, $-CH_2NH-$, or $-NHCH_2-$. L is preferably $-C(=V)-DR^{8'}-$.

V is suitably oxygen or sulfur. V is preferably oxygen.

D is suitably nitrogen, carbon or a CH group. D is preferably nitrogen.

$R^{1'}$ and $R^{2'}$ are suitably independently hydrogen, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkenyl, aryl, $(CH_2)_{d'}NR^{10'}R^{11'}$, $(CH_2)_{d'}NR^{10'}COR^{12'}$, $(CH_2)_{d'}NR^{10'}CO_2R^{13'}$, $(CH_2)_{d'}NR^{10'}SO_2R^{14'}$, $(CH_2)_{d'}CONR^{15'}R^{16'}$, hydroxy$C_{1-6}$alkyl, $C_{1-4}$alkoxyalkyl (optionally substituted by a $C_{1-4}$alkoxy or hydroxy group), $(CH_2)_{d'}CO_2C_{1-6}$alkyl, $(CH_2)_{e'}OC(O)R^{17'}$, $CR^{18'}{=}NOR^{19'}$, $CNR^{20'}{=}NOR^{19'}$, $COR^{21'}$, $CONR^{15'}R^{16'}$, $CONR^{15'}(CH_2)_{f'}OC_{1-4}$alkyl, $CONR^{15'}(CH_2)_{d'}CO_2R^{22'}$, $CONHNR^{23'}R^{24'}$, $CONR^{15'}SO_2R^{25'}$, $CO_2R^{26'}$, cyano, trifluoromethyl, $NR^{10'}R^{11'}$, $NR^{10'}COR^{12'}$, $NR^{27'}CO(CH_2)_{d'}NR^{27'}R^{28'}$, $NR^{27'}CONR^{27'}R^{28'}$, $NR^{10'}CO_2R^{13'}$, $NR^{10'}SO_2R^{14'}$, $N{=}CNR^{27'}NR^{27'}R^{28'}$, nitro, hydroxy, $C_{1-6}$alkoxy, hydroxy$C_{1-6}$alkoxy, $C_{1-6}$alkoxy$C_{1-6}$alkoxy, $OC(O)NR^{29'}R^{30'}$, $SR^{31'}$, $SOR^{32'}$, $SO_2R^{32'}$,

$SO_2NR^{33'}R^{34'}$, halogen, $C_{1-6}$alkanoyl, $CO_2(CH_2)_dOR^{35'}$, or $R^{1'}$ is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur. $R^{1'}$ and $R^{2'}$ are preferably hydrogen, $C_{1-6}$alkyl, hydroxy, or halogen.

$R^{3'}$ is suitably hydrogen, $C_{1-6}$alkyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkenyl, hydroxy$C_{1-6}$alkyl, $C_{1-6}$alkyl$OC_{1-6}$alkyl, $CONR^{36'}R^{37'}$, $CO_2R^{38'}$, cyano, aryl, trifluoromethyl, $NR^{39'}R^{40'}$, nitro, hydroxy, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, acyloxy, or halogen. $R^{3'}$ is preferably hydrogen, nitro, sulfamoyl or $C_{1-6}$alkylamino.

$R^{4'}$, $R^{5'}$, $R^{6'}$, $R^{7'}$, $R^{18'}$, $R^{19'}$, $R^{20'}$, $R^{21'}$, $R^{22'}$, $R^{23'}$, $R^{24'}$, $R^{27'}$, $R^{28'}$, $R^{31'}$, $R^{35'}$, $R^{36'}$, $R^{37'}$, $R^{38'}$, $R^{39'}$, and $R^{40'}$ are suitably independently hydrogen or $C_{1-6}$alkyl;

$R^{8'}$ is suitably hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group. $R^{8'}$ is preferably hydrogen.

$R^{9'}$ is suitably hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group.

$R^{10'}$ and $R^{11'}$ are suitably independently hydrogen or $C_{1-6}$alkyl, or $R^{10'}$ and $R^{11'}$ together with the nitrogen to which they are attached, forms a 5- to 6-membered heterocyclic ring, which may optionally be substituted by an oxo group, and, when there are six members, may optionally contain in the ring one oxygen or one sulfur atom.

$R^{12'}$ is suitably hydrogen, $C_{1-6}$alkyl, or $C_{1-4}$alkoxyalkyl.

$R^{13'}$, $R^{25'}$, and $R^{32'}$ are suitably independently $C_{1-6}$alkyl.

$R^{14'}$ is suitably $C_{1-6}$alkyl or phenyl.

$R^{15'}$ and $R^{16'}$ are suitably independently hydrogen or $C_{1-6}$alkyl, or $R^{15'}$ and $R^{16'}$ together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when there are 6 ring members, may optionally contain in the ring one oxygen or one sulfur atom.

$R^{17'}$ is suitably $C^{1-4}$alkyl, optionally substituted by $C_{1-6}$alkoxy.

$R^{26'}$ is suitably hydrogen or $C_{1-6}$alkyl optionally substituted with one or two substituents selected from $C_{1-6}$alkyl, $C_{1-6}$alkoxy, hydroxy, or $NR^{10'}R^{11'}$.

$R^{29'}$ and $R^{30'}$ are suitably independently hydrogen or $C_{1-6}$alkyl, or $R^{29'}$ and $R^{30'}$ together with the nitrogen to which they are attached form a 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or sulfur atom.

$R^{33'}$ and $R^{34'}$ are suitably independently hydrogen or $C_{1-6}$alkyl, or $R^{33'}$ and $R^{34'}$ together with the nitrogen to which they are attached form 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or sulfur atom.

a' and b' are independently 1, 2, or 3.

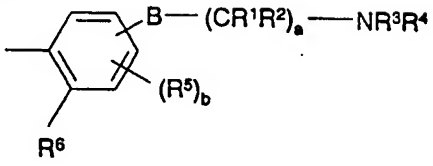
c' is suitably 0, 1, or 2.

d' is suitably 1, 2, 3, or 4.

e' is suitably 0, 1, 2, or 3.

f' is suitably 1, 2, or 3.

E suitably represents (a):




(a);

in which

B is suitably oxygen, $S(O)_c$, $CR^7=CR^8$, or $CR^7R^8$, or B is $NR^9$. B is preferably $CR^7R^8$, or oxygen. More preferably, B is $CH_2$ or oxygen.

$R^1$ and $R^2$ are suitably independently hydrogen or $C_{1-6}$alkyl; alternatively $B(CR^1R^2)_a$ is $OCR^1R^2CR^1(OH)CR^1R^2$ or $OCR^1R^2CR^1(OCOCH_3)CR^1R^2$. Preferably, $R^1$ and $R^2$ are hydrogen.

$R^3$ and $R^4$ are suitably independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, hydroxy, $OCOR^{12}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{13}$, and $NHCO_2R^{14}$. Preferably $R^3$ and $R^4$ are both $C_{1-6}$alkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur. More preferably, $R^3$ and $R^4$ are $C_{3-6}$alkyl, or together with the nitrogen to which they are attached form a 6-membered ring, optionally substituted with one or more of $C_{1-6}$alkyl, N-acetamido, or hydroxy. Most preferably, $R^3$ and $R^4$ are isopropyl or $R^3$ is isopropyl and $R^4$ is tert-butyl, or together with the nitrogen to which they are attached are 1-(2,2,6,6-tetramethylpiperidinyl), 1-(4-acetamido-2,2,6,6-tetramethylpiperidinyl), 1-(4-hydroxy-2,2,6,6-tetramethylpiperidinyl), or 1-(4-hydroxy-2,2,4,6,6-pentamethylpiperidinyl).

Preferably, B-$(CR^1R^2)_a$-$NR^3R^4$ is ortho to $R^5$, meta to L, and para to $R^6$, and $R^5$ is para to L.

$R^5$ is suitably hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{15}R^{16}$, $CO_2R^{17}$, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$, or halogen. $R^5$ is preferably $C_{1-6}$alkoxy,

$SC_{1-6}$alkyl, or halogen; more preferably methoxy, methylthio, or iodo, most preferably methoxy. When $R^5$ is methoxy, it is preferably para to L.

$R^6$ is suitably hydrogen, $C_{1-6}$alkyl, aryl, trifluoromethyl, hydroxy, $C_{1-6}$alkoxy, or halogen, or $R^6$ taken together with $R^{8'}$ forms a group D where D is $(CR^{22}R^{23})_e$ or D is $(CR^{22}R^{23})_f$-G where G is oxygen, sulfur, or $CR^{22}=CR^{23}$, $CR^{22}=N$, $=CR^{22}O$, $=CR^{22}S$, or $=CR^{22}$-$NR^{23}$. Preferably, $R^6$ is hydrogen.

$R^7$, $R^8$, $R^{10}$, $R^{11}$, $R^{15}$, $R^{16}$, $R^{17}$, $R^{20}$, $R^{21}$, $R^{22}$, and $R^{23}$ are independently hydrogen or $C_{1-6}$alkyl.

$R^9$ is hydrogen, $C_{1-6}$alkyl, or phenyl$C_{1-6}$alkyl.

$R^{12}$, $R^{13}$, $R^{14}$, $R^{18}$, and $R^{19}$ are independently $C_{1-6}$alkyl.

a is suitably 1, 2, 3, or 4. Preferably, a is 2 or 3, more preferably, a is 2 or 3 when B is oxygen and a is 2 when B is $CH_2$, most preferably, a is 2 when B is oxygen.

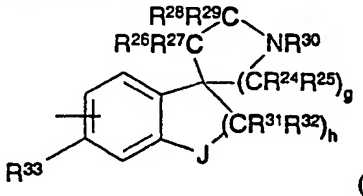
b is suitably 1 or 2. Preferably, b is 1.

c and d are suitably independently 0, 1, or 2.

e is suitably 2, 3, or 4.

f is suitably 0, 1, 2, or 3.

alternatively, E suitably represents (b):




(b);

$R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{31}$, and $R^{32}$ are suitably independently hydrogen or $C_{1-6}$alkyl. $R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{31}$, and $R^{32}$ are preferably hydrogen.

$R^{30}$ is suitably hydrogen, $C_{1-6}$alkyl, or $C_{3-7}$cycloalkyl. Preferably, $R^{30}$ is $C_{1-6}$alkyl, more preferably, $R^{30}$ is $C_{3-6}$alkyl, most preferably, $R^{30}$ is isopropyl.

$R^{33}$ is suitably hydrogen, $C_{1-6}$alkyl, trifluoromethyl, hydroxy, or halogen, or $R^{33}$ and $R^{8'}$ together form a group -K- where K is $(CR^{34}R^{35})_i$ or K is $(CR^{34}R^{35})_j$ -M and M is oxygen, sulfur, $CR^{34}=CR^{35}$, $CR^{34}=N$, or N=N. Preferably, $R^{33}$ is hydrogen.

J is suitably oxygen, $CR^{36}R^{37}$, or $NR^{38}$, or J is a group $S(O)_k$, Preferably, J is oxygen. Preferably, J is para to L.

$R^{34}$, $R^{35}$, $R^{36}$, $R^{37}$, $R^{38}$ are suitably independently hydrogen or $C_{1-6}$alkyl.

g is suitably 1, 2, or 3. Preferably, g is 2 or 3, more preferably 2.

h is suitably 1, 2, or 3. Preferably, h is 1.

i is suitably 2, 3, or 4.

j is suitably 0, 1, 2, or 3.

k is suitably 0, 1 or 2.

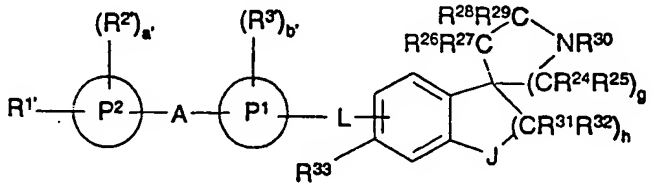
Known compounds overlapping with the scope of the instant invention are as follows.

A subgenus of formula (I) wherein: the basic nitrogen in moiety E may be optionally quaternized with $C_{1-6}$alkyl or is optionally present as the N-oxide; E is (b); J is $CH_2$; g is 1, 2, or 3; h is 1, 2, or 3; $R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{31}$, and $R^{32}$ are hydrogen; $R^{30}$ is hydrogen or $C_{1-6}$alkyl; $R^{33}$ is hydrogen, $C_{1-6}$alkyl, trifluoromethyl, or halogen; L is $CONR^{8'}$ or $NR^{9'}CO$; $R^{8'}$ and $R^{9'}$ are independently hydrogen or $C_{1-6}$alkyl; $P^1$ and $P^2$ are phenyl; A is CO, O or $S(O)_{0-2}$; $R^{1'}$ is hydrogen; $R^{2'}$ is hydrogen or 1, 2, or 3 of hydroxy, $C_{1-3}$alkyl, cyano, halogen, or trifluoromethyl; $R^{3'}$ is hydrogen or 1 or 2 of hydroxy, cyano, halogen, trifluoromethyl, $CONR^{36*}R^{37*}$, $COC_{1-5}$alkyl, $CO_2R^{38*}$, $C_{1-6}$alkoxy, or phenyl; and $R^{36*}$, $R^{37*}$, and $R^{38*}$ are independently hydrogen or $C_{1-6}$alkyl, has been described in WO 98/25604, published 18 June 1998, as chemokine receptor modulators.

Further, a subgenus of formula (I) wherein: the basic nitrogen in moiety E may be optionally quaternized with $C_{1-6}$alkyl or is optionally present as the N-oxide; E is (b); J is $CH_2$; g is 1, 2, or 3; h is 1, 2, or 3; $R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{31}$, and $R^{32}$ are hydrogen; $R^{30}$ is hydrogen or $C_{1-6}$alkyl; $R^{33}$ is hydrogen, $C_{1-6}$alkyl, trifluoromethyl, or halogen; L is $CH_2NH$; $P^1$ is heteroaryl, wherein heteroaryl is selected from the group consisting of benzimidazolyl, benzofuranyl, benzooxazolyl, furanyl, imidazolyl, indolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolyl, quinolyl, thiadiazolyl, thiazolyl, thienyl or triazolyl; A is CO, O or $S(O)_{0-2}$; $P^2$ is phenyl; $R^{1*}$ is hydrogen or one of hydroxy, cyano, halogen, trifluoromethyl, $NR^{10*}COR^{12*}$, $NR^{10*}CO_2R^{13*}$, $NR^{27*}CONHR^{28*}$, $NHS(O)_{0-2}R^{14*}$, $CONR^{15*}R^{16*}$, $COC_{1-5}$alkyl, $CO_2R^{26*}$, $C_{1-6}$alkoxy, $SR^{31*}$, $SOR^{32*}$, $SO_2R^{32*}$, or phenyl, or $R^{1*}$ is an optionally substituted heterocyclic ring selected from furanyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl or triazolyl; $R^{2*}$ is hydrogen or 1, or 2 of hydroxy, cyano, halogen, trifluoromethyl, $NR^{10*}COR^{12*}$, $NR^{10*}CO_2R^{13*}$, $NR^{27*}CONHR^{28*}$, $NHS(O)_{0-2}R^{14*}$, $CONR^{15*}R^{16*}$, $COC_{1-5}$alkyl, $CO_2R^{26*}$, $C_{1-6}$alkoxy, $SR^{31*}$, $SOR^{32*}$, $SO_2R^{32*}$, or phenyl; $R^{3'}$ is hydrogen or 1 or 2 of hydroxy, cyano, halogen, trifluoromethyl, $CONR^{36*}R^{37*}$, $COC_{1-5}$alkyl, $CO_2R^{38*}$, $C_{1-6}$alkoxy, or phenyl; $R^{10*}$, $R^{12*}$, $R^{15*}$, $R^{16*}$, $R^{27*}$, $R^{28*}$, $R^{31*}$, $R^{36*}$, $R^{37*}$, and $R^{38*}$ are independently hydrogen or $C_{1-6}$alkyl; $R^{13*}$ and $R^{32*}$ are independently $C_{1-6}$alkyl; $R^{14*}$ is $C_{1-6}$alkyl or phenyl; and $R^{26*}$ is hydrogen or $C_{1-6}$alkyl optionally substituted with one or two of hydroxy, has been

described in WO 98/25604, published 18 June 1998, as chemokine receptor modulators.

A preferred subgenus of the compounds of formula (I) are compounds of formula (Ia) in which $R^{1'}$, $R^{2'}$, $R^{3'}$, $P^1$, $P^2$, A, a', b', L, $R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{30}$, $R^{31}$, $R^{32}$, $R^{33}$, J, g, and h are defined as above:




Formula (Ia)

Among the preferred compounds of the invention are the following compounds:

N-[4-[2-(Dimethylamino)ethyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl)-4-phenoxybenzamide;

N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]]-4-phenoxybenzamide;

N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-3-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-(phenylmethyl)benzamide;

N-[2-[2-(Diethylamino)ethoxy]phenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2-(phenylmethyl)thiazole-4-carboxamide hydrochloride;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide Methiodide;

N-[1-[2-[Bis(1-methylethyl)amino]ethyl]-1,2,3,4-tetrahydroquinol-7-yl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(3-hydroxyphenoxy)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfinyl]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(2,4-dichlorophenyl)sulfinyl]-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-benzoylbenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(methylphenylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylthio)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfonyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfinyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(hydroxyimino)phenylmethyl]benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(hydroxyphenylmethyl)benzamide;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-benzoylbenzamide trifluoroacetate;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide; and

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide.

Among the more preferred compounds of this invention are the following compounds:

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide methiodide

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)oxy]-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)oxy]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylthio)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(hydroxyimino)phenylmethyl]benzamide;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-benzoylbenzamide trifluoroacetate;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide; and

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide.

Among the most preferred compounds of this invention are the following compounds:

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-benzoylbenzamide trifluoroacetate;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide; and

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide.

Among compounds excluded from this invention are the following compounds:

N-[2-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-phenoxybenzamide;

N-[2-[2-(Diethylamino)ethoxy]phenyl]-4-phenoxybenzamide;

N-[4-[2-(Diethylamino)ethoxy]phenyl]-3-phenoxybenzamide;

N-[2-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-3-phenoxybenzamide ;

N-[2-[2-(Diethylamino)ethoxy]phenyl]-3-phenoxybenzamide;

N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(phenylmethyl)benzamide; and

N-[2-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-(phenylmethyl)benzamide.

**Formulation of Pharmaceutical Compositions**

The pharmaceutically effective compounds of this invention (and the pharmaceutically acceptable salts thereof) are administered in conventional dosage forms prepared by combining a compound of this invention ("active ingredient") in an amount sufficient to treat COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, ("CCR5-mediated disease states") with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or

diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1000 mg. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The active ingredient may also be administered topically to a mammal in need of treatment or prophylaxis of CCR5 mediated disease states. The amount of active ingredient required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the disease state being treated and the mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of the active ingredient externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous or alcoholic solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

The active ingredient may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage amount of the active ingredient administered by inhalation is from about 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

In one aspect, this invention relates to a method of treating COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, all in mammals, preferably humans, which comprises administering to such mammal an effective amount of a CCR5 receptor modulator, in particular, a compound of this invention.

By the term "treating" is meant either prophylactic or therapeutic therapy. Such compound can be administered to such mammal in a conventional dosage form prepared by combining the compound of this invention with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The compound is administered to a mammal in need of treatment for COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic diseases, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, in an amount sufficient to decrease symptoms associated with these disease states. The route of administration may be oral or parenteral.

The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day of active ingredient. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day of active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of this invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

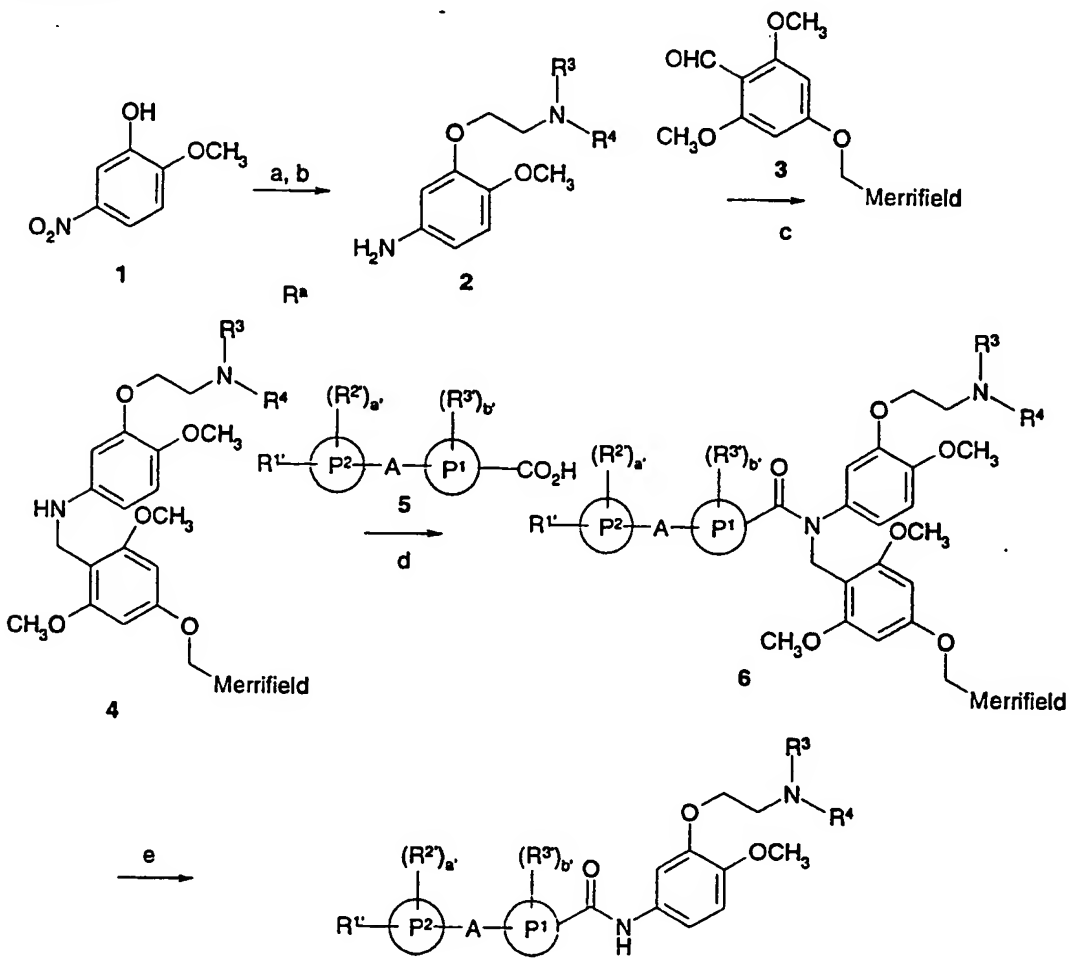
**Methods of Preparation**

Compounds of formula (I) are prepared by condensing suitably substituted aryl or heteroarylcarboxylic acids and suitably substituted anilines, which are commercially available or synthesized by methods known to the art from commercially available starting materials, using methods known to the art. For example, suitably substituted aryl or heteroarylcarboxylic acids are treated with a suitable reagent, such as thionyl chloride, at a suitable temperature, such as at reflux, to afford aryl or heteroarylcarbonyl chlorides, and the aryl- or heteroarylcarbonyl chlorides are condensed with suitably substituted anilines in the presence of a suitable base, such as diisopropylethylamine, in a suitable solvent, such as dichloromethane, to give compounds of formula (I). Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I-VI (published by Wiley-Interscience).

Compounds of formula (I) are also prepared using solid-phase chemistry as described in Scheme I and using the general method described in international patent application WO 99/01127, published 14 January 1999. For example, in Scheme 1, an appropriately substituted 3-(2-aminoethoxy)-4-methoxyaniline **I-2**, such as 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline, which is synthesized from the commercially available 2-methoxy-5-nitrophenol, **I-1**, according to the procedures described in WO 99/01127, is attached to a polymer support such as Merrifield resin-bound aldehyde **I-3**, which is synthesized according to the general protocol of Boojamra et al., (*J. Org. Chem.*, **1995**, 60, 5742-3) by reductive amination employing a reducing agent such as sodium triacetoxyborohydride in dimethylformamide with 1% acetic acid to give I-4. The resulting resin-bound aniline **I-4** is acylated with a commercially available or synthetically accessible, suitably substituted aryl or heteroaryl carboxylic acid **I-5**, for example 4-phenoxybenzoic acid, using, for example, N-bromo succinimide and triphenylphosphine in dichloromethane, or in dichloromethane in combination with dimethylformamide, in the presence of an organic base such as pyridine to afford **I-6**. For example, **1-4** is treated with a ten-fold excess of an equimolar mixture of a 3-aryl- or heteroaryl carboxylic acid, triphenylphosphine and N-bromosuccinimide, in a suitable solvent, such as dichloromethane, after which a ten-fold excess of a suitable base, such as pyridine, is added, and the mixture is gently agitated for a suitable time, for example, forty-eight hours, to afford the resin-bound amide **1-6**. Optionally, dimethylformamide may be added to the resulting mixture to increase the solubility of the 3-aryl- or heteroaryl carboxylic acid. Treatment of **I-6** with a mixture of a strong organic acid and organic solvent, such as trifluoroacetic

acid:dichloromethane:water (50:48:2), resulted in cleavage of the desired compound from the polymer support and afforded carboxanilide I-7, a compound of formula I.

Scheme I:




a) $Cl(CH_2)_2NR^3R^4$, $K_2CO_3$, $CH_3COCH_3$; (b) $H_2$, 5% Pd/C, MeOH; (c) Merrifield resin bound aldehyde (3); $NaBH(OAc)_3$, 1% HOAc, DMF; (d) aryl/heteroaryl carboxylic acid, NBS, $Ph_3P$, pyridine; (e) TFA, $CH_2Cl_2$, $H_2O$.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In the Examples, mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated.

## EXAMPLES

### Preparation 1

Preparation of 4-(Methylphenylamino)benzoic acid

A solution of ethyl 4-(methylphenylamino)benzoate (2.65 g, 10 mmol) (*Tetrahedron Lett.* **1997**, 38, 6359-6362) in tetrahydrofuran (50 mL), ethanol (25 mL), and water (5 mL) was treated with 1 N sodium hydroxide (84 mL) and heated to 50°C for 20 h. The mixture was reduced in volume *in vacuo*, diluted with water, and extracted three times with ethyl acetate. The aqueous phase was acidified with acetic acid to pH~6 and the white solid which precipitated was isolated by filtration, washed with water, and dried to give the title compound (1.95 g). MS (ES) m/e 227.8 $(M+H)^+$.

## Preparation 2

Preparation of 1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'-piperidin]-5-amine

a) 5- and 7-nitrospiro[benzofuran-3(2H),4'-piperidine]

A solution of 1'-methyl-5- and 7-nitrospiro[benzofuran-3(2H),4'-piperidine] (WO 96/11934) (3 g, 12 mmol) and diisopropylethylamine (2.5 g, 19 mmol) in 1,2-dichloroethane (80 mL) was treated with 1-chloroethyl chloroformate (2.3 g, 16 mmol) at RT, stirred for 1 h, and heated to reflux for 20 min. The mixture was cooled, concentrated *in vacuo*, and the residue was dissolved in methanol and heated to reflux for 2 h, concentrated *in vacuo*, and the residue was partitioned between dichloromethane (250 mL) and 5% sodium bicarbonate (50 mL). The organic phase was washed with 5% sodium bicarbonate (50 mL) and the combined aqueous phase was extracted with dichloromethane (2 X 50 mL). The combined organic phase was dried ($Na_2SO_4$) and concentrated to afford the title compound (2. 65 g).

b) 1'-(tert-butoxycarbonyl)-5-nitrospiro[benzofuran-3(2H),4'-piperidine]

A solution of the compound of Preparation 2(a)(2.65 g, 1.13 mmol) in tetrahydrofuran (300 mL) was treated with di-tert-butyl dicarbonate (2.6 g, 12 mmol) and stirred at RT for 16 h. The mixture was concentrated *in vacuo* and the residue was crystallized from methanol to afford the title compound (2.1 g).

c) 5-nitrospiro[benzofuran-3(2H),4'-piperidine]

A solution of the compound of Preparation 2(b)(2.1 g, 6.3 mmol) in dichloromethane (50 mL) and trifluoroacetic acid (10 mL) was kept at RT for 5 h, concentrated *in vacuo*, and the residue was partitioned between dichloromethane (300 mL) and 5% sodium bicarbonate. The organic phase was washed with 5% sodium bicarbonate and the combined aqueous washes were extracted with dichloromethane. The combined organic phase was dried ($Na_2SO_4$) and concentrated *in vacuo* to give the title compound (1.45 g). MS(ES) m/e 235.1 $[+H]^+$.

d) 1'-(1-methylethyl)-5-nitrospiro[benzofuran-3(2H),4'-piperidine]

A mixture of the compound of Preparation 2(c) (1.45 g, 6.2 mmol), powdered potassium carbonate (0.86 g, 6.2 mmol) and dimethylformamide (50 mL)

containing 2-iodopropane (1.1 g, 6.4 mmol) was stirred and heated to 50°C for 4 h, treated with 2-iodopropane (0.17 g, 1 mmol) at 50°C for 90 min, and treated with 2-iodopropane (0.1 g, 1 mmol) at 50°C for 2 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (200 mL) and water (20 mL). The organic phase was washed, dried ($MgSO_4$), concentrated *in vacuo*, and the residue was chromatographed (silica gel, 5% methanol:dichloromethane) to give the title compound (0.85 g).

e) 1'-(1-methylethyl)spiro[benzofuran-3(2H),4'-piperidin]-5-amine

A solution of the compound of Preparation 2(d) (0.78 g, 2.8 mmol) in methanol (250 mL) containing 10% palladium-on-carbon (0.375 g) was shaken in a hydrogen atmosphere (40 psi) for 40 min, filtered, and concentrated *in vacuo* to afford the title compound (0.6 g).

## Preparation 3

Preparation of 7-Amino-3,4-dihydro-N,N-bis(1-methylethyl)-1(2H)-quinolineethanamine

a) 3,4-dihydro-N,N-bis(1-methylethyl)-7-nitro-1(2H)-quinolineethanamine

Sodium carbonate (2.9 g, 27 mmol) was added to a mixture of 7-nitro-1,2,3,4-tetrahydroquinoline (1.2 g, 6.7 mmol) (United States Patent 5696133), 2-(diisopropylamino)ethyl chloride hydrochloride (4.0 g, 20 mmol), and ethanol (25 mL). The mixture was heated at reflux for 3 h, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography (silica gel, dichloromethane followed by 5% methanol:dichloromethane) to afford 1.4 g (68%) of the title compound as a yellow oil. MS(ES) m/e 306.1 $[M+H]^+$.

b) 7-amino-3,4-dihydro-N,N-bis(1-methylethyl)-1(2H)-quinolineethanamine

A mixture of the compound of Preparation 3(a) and 5% palladium-on-carbon in ethanol was hydrogenated at 50 psi. The mixture was filtered and concentrated *in vacuo* to afford the title compound.

## Preparation 4

Preparation of 2-(Phenylmethyl)-4-thiazolecarboxylic Acid

A solution of benzeneethanethioamide (1.0 g, 6.6 mmol) in dioxane (25 mL) was treated with bromopyruvic acid (1.1 g, 6.6 mmol) and heated to 90°C for 4 h. The mixture was diluted with water and the tan crystals which formed were collected by filtration to afford the title compound.

## Example 1

Preparation of N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide

a) 3-[2–(diethylamino)ethoxy]-4-methoxyaniline/[4-formyl-3,5-(dimethoxy)phenoxy]-Merrifield resin adduct

A mixture of [4-formyl-3,5-(dimethoxy)phenoxy]-Merrifield resin (Boojamra et al., *J. Org. Chem.* **1995**, 60, 5742-3), 3-[2-(diethylamino)ethoxy]-4-methoxyaniline (WO 95/15954), and sodium triacetoxyborohydride in dimethylformamide containing 1% acetic acid was shaken to afford the title adduct.

b) N-[3-[2–(diethylamino)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide/[4-formyl-3,5-(dimethoxy)phenoxy]-Merrifield resin adduct

The resin of Example 1(a) was placed in an Irori MicroKan and treated with a ten-fold molar excess of an equimolar mixture of 4-chlorocinnamic acid, N-bromosuccinimide, and triphenylphosphine in dichloromethane, followed by addition of a ten-fold excess of pyridine. The mixture was gently agitated for 48 h after which the resin was washed three-times, sequentially with dimethylformamide, dichloromethane, and methanol to afford the title adduct.

c) N-[3-[2–(diethylamino)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide

The resin of Example 1(b) was stirred in a mixture of trifluoroacetic acid:dichloromethane:water (50:48:2), filtered, and the filtrate concentrated *in vacuo* to afford the title compound. MS (ES) m/e 435.0 $(M+H)^+$.

**Examples 2-30**

Following the procedure of Example 1(a)-(c), except using 4-[(2-diisopropylamino)ethoxy]aniline (WO 99/01127), 4-[2-(diethylamino)ethoxy]aniline (*J. Med. Chem.* **1995**, 38, 1657-65), 3-[(2-diisopropylamino)ethoxy]aniline (WO 99/01127), 3-[(2-diisopropylamino)ethoxy]-4-methoxyaniline (WO 95/15954), 3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyaniline (WO 99/01127), and 3-[(3-diisopropylamino)propyl]-4-methoxyaniline (WO 99/01127) in addition to 3-[2-(diethylamino)ethoxy]-4-methoxyaniline, and except using 3-phenoxybenzoic acid, 4-(phenylmethyl)benzoic acid, 4-benzoylbenzoic acid, 4-[(4-chlorophenyl)sulfonyl]benzoic acid, 5-butylamino-4-phenoxy-3-(sulfamoyl)benzoic acid, 4-[(4-chlorophenyl)oxy]-3-nitrobenzoic acid, 2-[(4-carboxyphenyl)amino]quinoxaline, and 4-[(4-methylphenyl)sulfonyl]-3-nitrobenzoic acid in addition to 4-phenoxybenzoic acid, gave the title compounds:

N-[4-[2-[bis(1-methylethyl)amino]ethoxy]phenyl]]-4-phenoxybenzamide: MS (ES) m/e 433.2 $(M+H)^+$;

N-[4-[2-(diethylamino)ethoxy]phenyl]-4-phenoxybenzamide: MS (ES) m/e 405.2 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]phenyl]-4-phenoxybenzamide: MS (ES) m/e 433.2 $(M+H)^+$;

N-[3-[2-(diethylamino)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide: MS (ES) m/e 435.0 $(M+H)^+$;

N-[4-[2-[bis(1-methylethyl)amino]ethoxy]phenyl]-3-phenoxybenzamide: MS (ES) m/e 433.2 $(M+H)^+$;

N-[4-[2-[bis(1-methylethyl)amino]ethoxy]phenyl]-4-(phenylmethyl)benzamide: MS (ES) m/e 431.2 $(M+H)^+$;

N-[2-[2-(diethylamino)ethoxy]phenyl]-4-(phenylmethyl)benzamide: MS (ES) m/e 403.0 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-phenoxybenzamide: MS (ES) m/e 460.9 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide: MS (ES) m/e 502.9 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide: MS (ES) m/e 503.3 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-benzoylbenzamide: MS (ES) m/e 473.3 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide: MS (ES) m/e 515.3 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(phenylmethyl)benzamide: MS (ES) m/e 459.3 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide: MS (ES) m/e 501.3 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide: MS (ES) m/e 545.2 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide: MS (ES) m/e 543.2 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide: MS (ES) m/e 585.2 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide: MS (ES) m/e 613.3 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide: MS (ES) m/e 611.3 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide: MS (ES) m/e 653.3 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide: MS (ES) m/e 542.2 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide: MS (ES) m/e 540.2 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide: MS (ES) m/e 582.2 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide: MS (ES) m/e 514.4 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide: MS (ES) m/e 512.4 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide: MS (ES) m/e 554.2 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide: MS (ES) m/e 570.2 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide: MS (ES) m/e 568.3 $(M+H)^+$; and

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide: MS (ES) m/e 610.3 $(M+H)^+$.

## Example 31

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide 3-Phenoxybenzoyl chloride, prepared from 3-phenoxybenzoic acid (0.11 g, 0.5 mmol) and thionyl chloride ( 5 mL) heated to reflux for 30 min, concentrated *in vacuo* and concentrated *in vacuo* from dichloromethane, was dissolved in dichloromethane (5 mL) and treated with 3-[(2-diisopropylamino)ethoxy]-4-methoxyaniline (0.14 g, 0.5 mmol) and diisopropylethylamine (0.07 g, 0.5 mmol). The mixture was stirred at RT for 16 h, and washed twice with 5% sodium carbonate and with water. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford a residue that was chromatographed (silica gel, 1:1 ethyl acetate:hexane) to give the title compound (0.12 g). MS (ES) m/e 463.2 $(M+H)^+$.

## Example 32-35

Following the procedure of Example 31 except substituting 4-phenoxybenzoic acid, 4-(phenylmethyl)benzoic acid, 4-(phenylthio)benzoic acid, and 4-(phenylsulfonyl)benzoic acid (*Chim. Ther.* **1973**, 8, 340-1) for 3-phenoxybenzoic acid, gave the title compounds:

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide: MS (ES) m/e 463.0 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide: MS (ES) m/e 460.9 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylthio)benzamide: MS (ES) m/e 478.9 $(M+H)^+$; and

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfonyl)benzamide: MS (ES) m/e 510.7 $(M+H)^+$.

## Example 36

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(3-hydroxyphenoxy)benzamide A solution of 4-(3-hydroxyphenoxy)benzoic acid (0.23 g, 1 mmol), 3-[(2-diisopropylamino)ethoxy]-4-methoxyaniline (0.27 g, 1 mmol), and BOP reagent (0.44 g, 1 mmol) in acetonitrile (20 mL) was treated with triethylamine (0.2 g, 2 mmol) and stirred at RT for 16 h. The mixture was diluted with dichloromethane and filtered. The filtrate was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to afford a residue that was purified by HPLC (ODS-A, 20 X 50 mm, A:acetonitrile B:water-0.1% trifluoroacetic acid, 10-90% during 10 min, UV detection at 254 nm) to afford the title compound. MS (ES) m/e 478.8 $(M+H)^+$.

## Examples 37-43

Following the procedure of Example 36, except substituting 4-[(4-chlorophenyl)sulfinyl]-3-nitrobenzoic acid, 4-[(2,4-dichlorophenyl)sulfinyl]-3-nitrobenzoic acid, 4-benzoylbenzoic acid, 3-benzoylbenzoic acid, the compound of Preparation 1, 4-(phenylamino)benzoic acid, and 4-(phenylsulfinyl)benzoic acid (*Synthesis* **1990**, 847-9) for 4-(3-hydroxyphenoxy)benzoic acid, afforded the title compounds:

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfinyl]-3-nitrobenzamide: MS (ES) m/e 573.7 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(2,4-dichlorophenyl)sulfinyl]-3-nitrobenzamide: MS (ES) m/e 607.7 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide: MS (ES) m/e 475.3 $(M+H)^+$;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-benzoylbenzamide: MS (ES) m/e 474.9 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(methylphenylamino)benzamide: MS (ES) m/e 475.9 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylamino)benzamide: MS (ES) m/e 462.0 $(M+H)^+$; and

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfinyl)benzamide: MS (ES) m/e 494.7 $(M+H)^+$.

## Example 44

Preparation of N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-phenoxybenzamide Following the procedure of Example 36, except substituting 4-phenoxybenzoic acid for 4-(3-hydroxyphenoxy)benzoic acid and 3-[(3-diisopropylamino)propyl]-4-methoxyaniline for 3-[(2-diisopropylamino)ethoxy]-4-methoxyaniline, afforded the title compound. MS (ES) m/e 461.3 $(M+H)^+$.

## Example 45

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(hydroxyimino)phenylmethyl]benzamide A solution of the compound of Example 39 (0.24 g, 0.5 mmol), hydroxylamine hydrochloride (0.17 g), and triethylamine (0.24 mL) in ethanol (10 mL) was heated to reflux for 20 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and water to give the title compound. MS (ES) m/e 490.0 $(M+H)^+$.

**Example 46**

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(hydroxyphenylmethyl)benzamide A mixture of the compound of Example 39 (0.24 g, 0.5 mmol), ethanol (21 mL), water (7 mL), methanol (5 mL), and dichloromethane (5 mL) was treated with sodium borohydride (0.13 g, 3.5 mmol) and stirred at RT for 2 h. The mixture was diluted with water, reduced in volume *in vacuo*, and extracted three times with dichloromethane. The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (40 mg). MS (ES) m/e 477.2 $(M+H)^+$.

**Example 47**

Preparation of N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-benzoylbenzamide trifluoroacetate A solution of 4-benzoylbenzoic acid (55 mg, 0.254 mmol), the compound of Preparation 2(e) (60 mg, 0.24 mmol), and BOP reagent (108 mg, 0.24 mmol) in acetonitrile (5 mL) was treated with triethylamine (50 mg, 0.5 mmol) and stirred at RT for 16 h. The mixture was quenched with brine and extracted with ethyl acetate. The organic extract was washed with 5% sodium carbonate and with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by HPLC (ODS-A, 20 X 50 mm, A:acetonitrile B:water-0.1% trifluoroacetic acid, 10-90% during 10 min, UV detection at 254 nm) to give the title compound. MS (ES) m/e 455.1 $(M+H)^+$.

**Examples 48-49**

Preparation of N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide and N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide

Following the procedure of Example 47, except substituting 4-phenoxybenzoic acid and 4-(phenylthio)benzoic acid for 4-benzoylbenzoic acid, gave the title compounds:

N-[1'-(1-methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide: MS (ES) m/e 443.1 $(M+H)^+$; and

N-[1'-(1-methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide: MS (ES) m/e 459.1 $(M+H)^+$.

**Example 50**

Preparation of N-[1-[2-[Bis(1-methylethyl)amino]ethyl]-1,2,3,4-tetrahydroquinol-7-yl]-4-phenoxybenzamide Following the procedure of Example 31, except substituting 4-phenoxybenzoic acid for 3-phenoxybenzoic acid and substituting the compound of Preparation 3(b) for 3-[(2-diisopropylamino)ethoxy]-4-methoxyaniline, gave the title compound. MS (ES) m/e 472.2 $(M+H)^+$.

**Example 51**

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide Methiodide The compound of Example 32 (93 mg, 0.2 mmol) in methanol (3 mL) was treated with iodomethane (8 mL), maintained at RT for 4 d, concentrated *in vacuo*, and the residue was triturated with ethyl acetate and then with1:1 ethyl acetate:ether. The residue was stirred with 1:1 ethyl acetate:ether for several hours and filtered to afford the title compound. MS (ES) m/e 477 $(M+H)^+$.

**Example 52**

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2-(phenylmethyl)thiazole-4-carboxamide hydrochloride

Following the procedure of Example 31, except substituting the compound of Preparation 4 for 3-phenoxybenzoic acid, afforded the title compound. MS (ES) m/e 468.0 $(M+H)^+$.

**Biological Data:**

CCR5 Receptor Binding Assay CHO cell membranes ($0.25 \times 10^6$ cell equivalents) derived from CHO cells stably transfected with CCR5 were incubated with 0.3 $^{125}$I-RANTES in a 96 well plate for 45 min at room temperature (final reaction volume 200 ul). The reaction was terminated by filtration and the filters (GF/C) were washed twelve times with a solution of phosphate buffered saline containing 0.1 % bovine serum albumin and 0.05 % $NaN_3$. The radioactivity bound to filters was measured by liquid scintillation spectrometry. Non-specific binding was determined in the presence of unlabelled RANTES (10 or 30 nM) and averages 30-50% of total binding.

CCR5 Receptor Functional Assay

The cellular functional assay used to assess antagonist activity of compounds was RANTES-induced $Ca^{2+}$ mobilization in RBL 2H3 cells stably expressing the hCCR5 receptor (RBL 2H3 hCCR5). Agonist activity is determined by $Ca^{2+}$ mobilization in the same cells which is inhibitable by a selective CCR5 antagonist. Cells were grown to 80-100% confluency in T-150 flasks and washed with phosphate-buffered saline. Cells were lifted from the flasks by treating with 3 mL of 1 mM EDTA for 3 min at room temperature and diluting to $2 \times 10^6$ cells/mL with Krebs Ringer Henseleit buffer (KRH; 118 mM NaCl, 4.6 mM KCl, 25 mM $NaHCO_3$, 1 mM $KH_2PO_4$ and 11 mM glucose) containing 5

mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% BSA and centrifuged at 200g for 3 min. Cells were resuspended at 2 X $10^6$ cells/mL in the same buffer with 2 μM Fura-2AM, and incubated for 35 min at 37° C. Cells were centrifuged at 200 x g for 3 min and resuspended in the same buffer without Fura-2AM, then incubated for 15 min at 37° C to complete the hydrolysis of intracellular Fura-2AM, and then centrifuged as before. Cells ($10^6$ cells/mL) were resuspended in cold KRH with 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% gelatin and maintained on ice until assayed. For antagonist studies, aliquots (2 mL) of cells were prewarmed at 37° C for 5 min in 3 mL plastic cuvettes and fluorescence measured in a fluorometer (Johnson Foundation Biomedical Group, Philadelphia, PA, USA) with magnetic stirring and temperature maintained at 37° C. Excitation was set at 340 nm and emission set at 510 nm. Various concentrations of antagonists or vehicle were added and fluorescence monitored for ~15 sec to ensure that there was no change in baseline fluorescence, followed by the addition of 33 nM RANTES. Maximal $Ca^{2+}$ attained after 33 nM RANTES stimulation was calculated as described by Grynkiewicz *et al.*, (1985). The percent of maximal RANTES-induced $Ca^{2+}$ was determined for each concentration of antagonist and the $IC_{50}$, defined as the concentration of test compound that inhibits 50% of the maximal 33 nM RANTES response, obtained from the concentration-response curves (5-7 concentrations of antagonists).

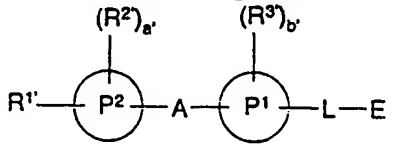
The compounds of this invention show CCR5 receptor modulator activity having $IC_{50}$ values in the range of 0.0001 to 100 μM. The full structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of this invention are modulators of the CCR5 receptor and which bind thereto with an $IC_{50}$ value in the range of 0.0001 to 100 μM.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration it is believed that one skilled in the art can, given the preceding description, utilize the present invention to its fullest extent. Therefore any examples are to be construed as merely illustrative and not a limitation on the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A method of treating a CCR5-mediated disease state in mammals which comprises administering to a mammal in need of such treatment, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:




Formula I

wherein:

the basic nitrogen in moiety E may be optionally quaternized with $C_{1-6}$alkyl or is optionally present as the N-oxide;

$P^1$ and $P^2$ are independently phenyl, fused bicyclic aryl, a monocyclic heterocyclic ring of 5- to 7-members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, or a fused bicyclic heterocyclic ring of 8 to 11-members containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

A is $C(R^{4'})_2$, $CR^{4'}(OR^{5'})$, CO, $C{=}NOR^{6'}$, $NR^{7'}$, oxygen, or $S(O)_{c'}$;

L is a group of formula $-C(=V)-DR^{8'}-$, $-DR^{9'}-C(=V)-$, $-CH_2NH-$, or $-NHCH_2-$;

V is oxygen or sulfur;

D is nitrogen, carbon, or a CH group,

$R^{1'}$ and $R^{2'}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkenyl, aryl, $(CH_2)_{d'}NR^{10'}R^{11'}$, $(CH_2)_{d'}NR^{10'}COR^{12'}$, $(CH_2)_{d'}NR^{10'}CO_2R^{13'}$, $(CH_2)_{d'}NR^{10'}SO_2R^{14'}$, $(CH_2)_{d'}CONR^{15'}R^{16'}$, hydroxy$C_{1-6}$alkyl, $C_{1-4}$alkoxyalkyl (optionally substituted by a $C_{1-4}$alkoxy or hydroxy group), $(CH_2)_{d'}CO_2C_{1-6}$alkyl, $(CH_2)_{e'}OC(O)R^{17'}$, $CR^{18'}{=}NOR^{19'}$, $CNR^{20'}{=}NOR^{19'}$, $COR^{21'}$, $CONR^{15'}R^{16'}$, $CONR^{15'}(CH_2)_{f'}OC_{1-4}$alkyl, $CONR^{15'}(CH_2)_{d'}CO_2R^{22'}$, $CONHNR^{23'}R^{24'}$, $CONR^{15'}SO_2R^{25'}$, $CO_2R^{26'}$, cyano, trifluoromethyl, $NR^{10'}R^{11'}$, $NR^{10'}COR^{12'}$, $NR^{27'}CO(CH_2)_{d'}NR^{27'}R^{28'}$, $NR^{27'}CONR^{27'}R^{28'}$, $NR^{10'}CO_2R^{13'}$, $NR^{10'}SO_2R^{14'}$, $N{=}CNR^{27'}NR^{27'}R^{28'}$, nitro, hydroxy, $C_{1-6}$alkoxy, hydroxy$C_{1-6}$alkoxy, $C_{1-6}$alkoxy$C_{1-6}$alkoxy, $OC(O)NR^{29'}R^{30'}$, $SR^{31'}$, $SOR^{32'}$, $SO_2R^{32'}$, $SO_2NR^{33'}R^{34'}$, halogen, $C_{1-6}$alkanoyl, $CO_2(CH_2)_{d'}OR^{35'}$, or $R^{1'}$ is an optionally substituted 5 to 7-

membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;

$R^{3'}$ is hydrogen, $C_{1-6}$alkyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkenyl, hydroxy$C_{1-6}$alkyl, $C_{1-6}$alkyl$OC_{1-6}$alkyl, $CONR^{36'}R^{37'}$, $CO_2R^{38'}$, cyano, aryl, trifluoromethyl, $NR^{39'}R^{40'}$, nitro, hydroxy, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, acyloxy, or halogen;

$R^{4'}$, $R^{5'}$, $R^{6'}$, $R^{7'}$, $R^{18'}$, $R^{19'}$, $R^{20'}$, $R^{21'}$, $R^{22'}$, $R^{23'}$, $R^{24'}$, $R^{27'}$, $R^{28'}$, $R^{31'}$, $R^{35'}$, $R^{36'}$, $R^{37'}$, $R^{38'}$, $R^{39'}$, and $R^{40'}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{8'}$ is hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group;

$R^{9'}$ is hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group;

$R^{10'}$ and $R^{11'}$ are independently hydrogen or $C_{1-6}$alkyl, or $R^{10'}$ and $R^{11'}$ together with the nitrogen to which they are attached, forms a 5- to 6-membered heterocyclic ring, which may optionally be substituted by an oxo group, and, when there are six members, may optionally contain in the ring one oxygen or one sulfur atom;

$R^{12'}$ is hydrogen, $C_{1-6}$alkyl, or $C_{1-4}$alkoxyalkyl;

$R^{13'}$, $R^{25'}$, and $R^{32'}$ are independently $C_{1-6}$alkyl;

$R^{14'}$ is $C_{1-6}$alkyl or phenyl;

$R^{15'}$ and $R^{16'}$ are independently hydrogen or $C_{1-6}$alkyl, or $R^{15'}$ and $R^{16'}$ together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when there are 6 ring members, may optionally contain in the ring one oxygen or one sulfur atom;

$R^{17'}$ is $C^{1-4}$alkyl, optionally substituted by $C_{1-6}$alkoxy;

$R^{26'}$ is hydrogen or $C_{1-6}$alkyl optionally substituted with one or two substituents selected from $C_{1-6}$alkyl, $C_{1-6}$alkoxy, hydroxy, or $NR^{10'}R^{11'}$;

$R^{29'}$ and $R^{30'}$ are independently hydrogen or $C_{1-6}$alkyl, or $R^{29'}$ and $R^{30'}$ together with the nitrogen to which they are attached form a 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or sulfur atom;

$R^{33'}$ and $R^{34'}$ are independently hydrogen or $C_{1-6}$alkyl, or $R^{33'}$ and $R^{34'}$ together with the nitrogen to which they are attached form 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or one sulfur atom;

a' and b' are independently 1, 2, or 3;

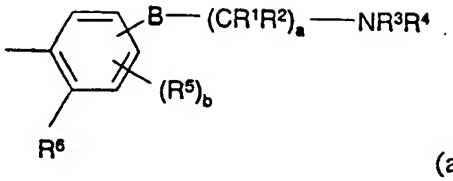
c' is 0, 1, or 2;

d' is 1, 2, 3, or 4;

e' is 0, 1, 2, or 3;

f' is 1, 2, or 3;

E represents (a):




(a);

in which

B is oxygen, $S(O)_c$, $CR^7=CR^8$, or $CR^7R^8$, or B is $NR^9$;

$R^1$ and $R^2$ are independently hydrogen or $C_{1-6}$alkyl; alternatively $B(CR^1R^2)_a$ is $OCR^1R^2CR^1(OH)CR^1R^2$ or $OCR^1R^2CR^1(OCOCH_3)CR^1R^2$;

$R^3$ and $R^4$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, hydroxy, $OCOR^{12}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{13}$, and $NHCO_2R^{14}$;

$R^5$ is hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{15}R^{16}$, $CO_2R^{17}$, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$ or halogen;

$R^6$ is hydrogen, $C_{1-6}$alkyl, aryl, trifluoromethyl, hydroxy, $C_{1-6}$alkoxy or halogen, or $R^6$ taken together with $R^{8'}$ forms a group D where D is $(CR^{22}R^{23})_e$ or D is $(CR^{22}R^{23})_f$-G where G is oxygen, sulfur or $CR^{22}=CR^{23}$, $CR^{22}=N$, $=CR^{22}O$, $=CR^{22}S$, or $=CR^{22}$-$NR^{23}$;

$R^7$, $R^8$, $R^{10}$, $R^{11}$, $R^{12}$, $R^{15}$, $R^{16}$, $R^{17}$, $R^{20}$, $R^{21}$, $R^{22}$, and $R^{23}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^9$ is hydrogen, $C_{1-6}$alkyl, or phenyl$C_{1-6}$alkyl;

$R^{13}$, $R^{14}$, $R^{18}$, and $R^{19}$ are independently $C_{1-6}$alkyl;

a is 1, 2, 3, or 4;

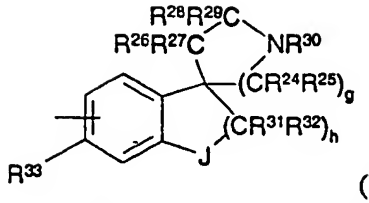
b is 1 or 2;

c and d are independently 0, 1 or 2;

e is 2, 3 or 4;

f is 0, 1, 2 or 3;

alternatively, E represents (b):



(b);

$R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{31}$, and $R^{32}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{30}$ is hydrogen, $C_{1-6}$alkyl, or $C_{3-7}$cycloalkyl;

$R^{33}$ is hydrogen, $C_{1-6}$alkyl, trifluoromethyl, hydroxy, or halogen, or $R^{33}$ and $R^{8'}$ together form a group -K- where K is $(CR^{34}R^{35})_i$ or K is $(CR^{34}R^{35})_j$ -M and M is oxygen, sulfur, $CR^{34}=CR^{35}$, $CR^{34}=N$, or N=N;

J is oxygen, $CR^{36}R^{37}$, or $NR^{38}$, or J is a group $S(O)_k$;

$R^{34}$, $R^{35}$, $R^{36}$, $R^{37}$, and $R^{38}$ are independently hydrogen or $C_{1-6}$alkyl;

g is 1, 2 or 3;

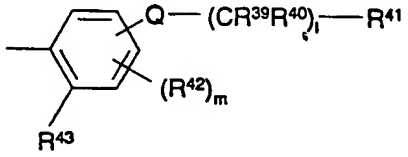
h is 1, 2 or 3;

i is 2, 3, or 4;

j is 0, 1, 2, or 3;

k is 0, 1 or 2;

alternatively, E represents (c):



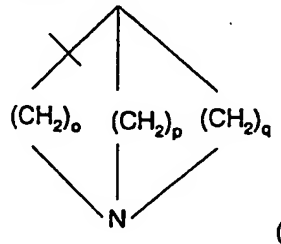
(c);

in which:

Q is oxygen, $S(O)_n$, $CR^{44}=CR^{45}$, $CR^{44}R^{45}$, or Q is $NR^{46}$;

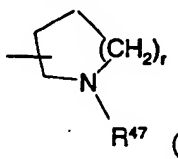
$R^{39}$ and $R^{40}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{41}$ is a group of formula (d):



(d)

or $R^{41}$ is a group of formula (e):



(e)

$R^{42}$ is hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{48}R^{49}$, $CO_2R^{50}$, trifluoromethyl, $NHCO_2R^{51}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_sR^{52}$, $SO_2NR^{53}R^{54}$, or halogen;

$R^{43}$ is hydrogen or $R^{43}$ together with $R^{8'}$ forms a group R where R is $CR^{55}=CR^{56}$, $CR^{55}=CR^{56}CR^{55}R^{56}$, or $(CR^{55}R^{56})_t$;

$R^{44}$, $R^{45}$, $R^{46}$, $R^{48}$, $R^{49}$, $R^{50}$, $R^{53}$, $R^{54}$, $R^{55}$, and $R^{56}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{47}$ is hydrogen, $C_{1-6}$alkyl, or $C_{3-7}$ cycloalkyl;

$R^{51}$ and $R^{52}$ are independently $C_{1-6}$alkyl;

l is 0, 1, 2, or 3;

m is 1 or 2;

n is 0, 1, or 2

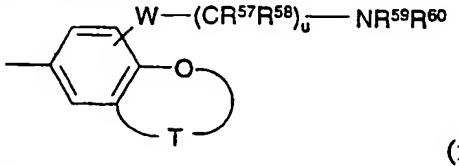
o, p, and q are independently integers having the value 1, 2, or 3;

r is 0,1, 2, or 3;

s is 0, 1, or 2;

t is 2 or 3;

alternatively, E represents (f):




(f);

$R^{57}$ and $R^{58}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{59}$ and $R^{60}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{61}R^{62}$, $NR^{61}R^{62}$, hydroxy, $OCOR^{63}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{64}$, and $NHCO_2R^{65}$;

T is $-(CR^{66}R^{67})_v-$ or $-O(CR^{66}R^{67})_w-$;

W is oxygen, $S(O)_x$, $NR^{68}$, or W is $CR^{69}=CR^{70}$ or $CR^{69}R^{70}$;

$R^{61}$, $R^{62}$, $R^{63}$, $R^{66}$, $R^{67}$ $R^{68}$, $R^{69}$, and $R^{70}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{64}$ and $R^{65}$ are independently $C_{1-6}$alkyl;

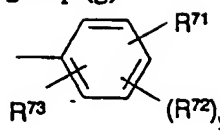
u is 1 to 4;

v is 2 or 3;

w is 1, 2, or 3;

x is 0, 1 or 2;

alternatively, E represents a group (g):



(g);

$R^{71}$ is an optionally substituted 5 to 7-membered saturated or partially saturated heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur or $R^{71}$ is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom and optionally a further heteroatom selected from oxygen, nitrogen or sulfur;

$R^{72}$ is hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{74}R^{75}$, $CO_2R^{76}$, trifluoromethyl, $NHCO_2R^{77}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_zR^{78}$, $SO_2NR^{79}R^{80}$, or halogen;

$R^{73}$ is hydrogen, $C_{1-6}$alkyl, hydroxy, $C_{1-6}$alkoxy or halogen, or $R^{73}$ and $R^{8'}$ taken together from a group -X- where X is $(CR^{81}R^{82})_{aa}$ or X is $(CR^{81}R^{82})_{ab}$-Y and Y is oxygen, sulfur or $CR^{81}=CR^{82}$;

$R^{74}$, $R^{75}$, $R^{76}$, $R^{79}$, $R^{80}$, $R^{81}$, and $R^{82}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{77}$ and $R^{78}$are independently $C_{1-6}$alkyl;

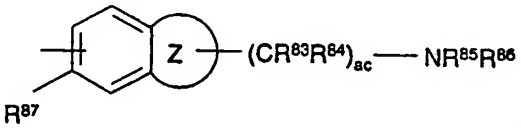
y is 1 or 2;

z is 0, 1, or 2;

aa is 2, 3 or 4;

ab is 0, 1, 2 or 3;

alternatively, E represents group (h):



(h);

$R^{83}$ and $R^{84}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{85}$ and $R^{86}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{88}R^{89}$, $NR^{90}R^{91}$, hydroxy, $OCOR^{92}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{93}$, and $NHCO_2R^{94}$;

$R^{87}$ is hydrogen or $C_{1-6}$alkyl, $C_{1-6}$alkoxy, or halogen, or $R^{87}$ together with $R^{8'}$ forms a group -AA- where AA is $(CR^{95}R^{96})_{ad}$ or AA is $(CR^{95}=CR^{96})_{ae}$-AB and AB is oxygen, sulfur, $CR^{95}=CR^{96}$, $CR^{95}=N$, $CR^{95}NR^{96}$ or N=N;

Z is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

$R^{88}$, $R^{89}$, $R^{90}$, $R^{91}$, $R^{92}$, $R^{95}$, and $R^{96}$ are independently hydrogen or $C_{1-6}$alkyl;

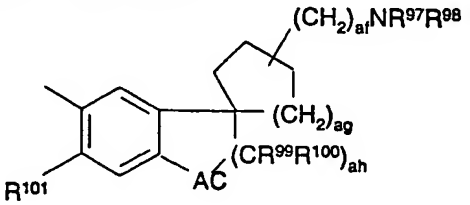
$R^{93}$ and $R^{94}$ are independently $C_{1-6}$alkyl;

ac is 0 to 4;

ad is 1, 2 or 3;

ae is 0, 1 or 2;

alternatively, E represents group (i):




(i);

$R^{97}$ and $R^{98}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{102}R^{103}$, $NR^{104}R^{105}$, hydroxy, $OCOR^{106}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2$ $R^{107}$, and $NHCO_2R^{108}$;

$R^{99}$ and $R^{100}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{101}$ is hydrogen or $C_{1-6}$alkyl or $R^{101}$ and $R^{8'}$ together form a group -AD- where AD is $(CR^{109}R^{110})_{ai}$ or AD is $(CR^{109}R^{110})_{aj}$-AE and AE is oxygen, sulfur or $CR^{109}=CR^{110}$;

AC is oxygen, $CR^{111}R^{112}$ or $NR^{113}$ or AC is a group $S(O)_{ak}$;

$R^{102}$, $R^{103}$, $R^{104}$, $R^{105}$, $R^{106}$, $R^{109}$, $R^{110}$, $R^{111}$, $R^{112}$, and $R^{113}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{107}$ and $R^{108}$ are independently $C_{1-6}$alkyl;

af is 0, 1, 2, 3, or 4;

ag is 1, 2, or 3;

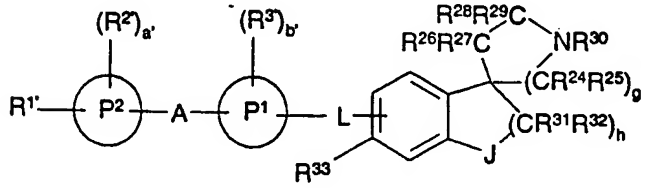
ah is 1, 2, 3 or 4;

ai is 2, 3 or 4;

aj is 0, 1, 2, or 3; and

ak is 0, 1 or 2.

2. The method of claim 1 wherein the compound of formula (I) is selected from a subgenus of formula (Ia) or a pharmaceutically acceptable salt thereof:



Formula (Ia)

wherein:
$R^{1'}$, $R^{2'}$, $R^{3'}$, $P^1$, $P^2$, A, a', b', L, $R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{30}$, $R^{31}$, $R^{32}$, $R^{33}$, J, g, and h are defined in claim 1.

3. The method as claimed in claim 1 wherein the compound is selected from:

N-[4-[2-(Dimethylamino)ethyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl)-4-phenoxybenzamide;

N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]]-4-phenoxybenzamide;

N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-3-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-(phenylmethyl)benzamide;

N-[2-[2-(Diethylamino)ethoxy]phenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2-(phenylmethyl)thiazole-4-carboxamide hydrochloride;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide Methiodide;

N-[1-[2-[Bis(1-methylethyl)amino]ethyl]-1,2,3,4-tetrahydroquinol-7-yl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(3-hydroxyphenoxy)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfinyl]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(2,4-dichlorophenyl)sulfinyl]-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-benzoylbenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(methylphenylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylthio)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfonyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfinyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(hydroxyimino)phenylmethyl]benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(hydroxyphenylmethyl)benzamide;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-benzoylbenzamide trifluoroacetate;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide; and

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide;

or a pharmaceutically acceptable salt thereof.

4. The method of claim 1 wherein the CCR5-mediated disease state is selected from COPD, asthma and atopic disorders, rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic disease, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV.

5. A compound of formula (I) selected from:

N-[4-[2-(Dimethylamino)ethyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl)-4-phenoxybenzamide;

N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]]-4-phenoxybenzamide;

N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-3-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-(phenylmethyl)benzamide;

N-[2-[2-(Diethylamino)ethoxy]phenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2-(phenylmethyl)thiazole-4-carboxamide hydrochloride;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide Methiodide;

N-[1-[2-[Bis(1-methylethyl)amino]ethyl]-1,2,3,4-tetrahydroquinol-7-yl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(3-hydroxyphenoxy)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfinyl]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(2,4-dichlorophenyl)sulfinyl]-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-benzoylbenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(methylphenylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylthio)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfonyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfinyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(hydroxyimino)phenylmethyl]benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(hydroxyphenylmethyl)benzamide;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-benzoylbenzamide trifluoroacetate;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide; and

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US99/17121

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 31/165; C07D 235/56
US CL : 514/618, 620, 621, 622; 564/168, 169, 171
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. 514/618, 620, 621, 622, 564/168, 169, 171

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN/CAS, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim |
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| A | US 4,263,039 A (NOGUCHI et al.) 21 April 1981 (21.04.81), see entire document. | 1-5 |

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Form PCT/ISA/210 (second sheet)(July 1992)*

CORRECTED VERSION*

PCT

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 31/165, C07D 235/56

A1

(11) International Publication Number: WO 00/06146

(43) International Publication Date: 10 February 2000 (10.02.00)

(21) International Application Number: PCT/US99/17121

(22) International Filing Date: 28 July 1999 (28.07.99)

(30) Priority Data:

| | | |
|---|---|---|
| 60/094,406 | 28 July 1998 (28.07.98) | US |
| 60/134,157 | 14 May 1999 (14.05.99) | US |


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(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published**

*With international search report.*

*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: COMPOUNDS AND METHODS

(57) Abstract

This invention relates to substituted anilide compounds which are modulators, agonists or antagonists, of the CCR5 receptor. In addition, this invention relates to the treatment and prevention of disease states mediated by CCR5.

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# COMPOUNDS AND METHODS

## FIELD OF THE INVENTION

This invention relates to substituted anilide compounds which are modulators, agonists or antagonists, of the CC chemokine receptor CC-CKR5 now designated as CCR5 (*Nature Medicine* **1996**, *2*, 1174-8). In addition, this invention relates to the treatment and prevention of disease states mediated by CCR5.

## BACKGROUND OF THE INVENTION

T cells are not only key regulators of the immune response to infectious agents but are believed critical for the initiation and maintenance of the inflammatory reaction in a variety of chronic diseases. Increased numbers or enhanced activation state of T cells, especially CD4+ T cells, have been demonstrated in the synovium of individuals with rheumatoid arthritis (M.J. Elliott and R. N. Maini, Int. Arch. Allergy Immunol. 104: 112-1125, 1994), in the bronchial mucosa of asthmatics (C.J. Corrigan and A.B. Kay, Immunol. Today 13:501-506, 1992), in the lesions of multiple sclerosis (R. Martin and H. F. McFarland, Crit. Rev. Clin. Lab. Sci. 32: 121-182, 1995), in psoriatic lesions (J.L. Jones, J. Berth-Jone, A. Fletcher and P.E. Hutchinson, J. Pathol. 174: 77-82, 1994) and in the fatty streaks of atherosclerosis (R. Ross, Annu. Rev. Physiol. 57: 791-804, 1995).

T cells, as well as other inflammatory cells, will migrate into tissues in response to the production of a variety of chemotactic factors. Among these factors are a superfamily of 8-12 kDa proteins known as the chemokines. These proteins share structural features such as the presence of 3-4 conserved cysteine residues. RANTES, which stands for Regulated upon Activation Normal T cell Expressed and Secreted, is an 8 kDa protein member of CC branch of the chemokine family. These proteins recruit and activate immune and inflammatory cells through an interaction with G-protein coupled receptors. The CC branch is defined by the absence of an intervening amino acid residue between the first two cysteine residues and members of this family predominately elicit the migration of mononuclear cells, eosinophils and basophils (M. Baggiolini, B. Dewald, and B. Moser, Adv. Immunol. 55: 97-179, 1994; and J.J. Oppenheim, C.O.C. Zachariae, N. Mukaida, and K. Matsushima, Annu. Rev. Immunol. 9: 617-648, 1991).

RANTES potently produces chemotaxis of T cells, basophils, eosinophils, monocytes and mast cells. RANTES was originally identified as gene product induced late after antigen activation of T-cells (T.J. Schall, J. Jongstra, B.J. Dyer, J. Jorgensen, et al., J. Immunol. 141:1018-1025, 1988), however, RANTES has been shown to be synthesized and secreted by a diverse group of cells that include

epithelial and endothelial cells (C. Stellato, L.A. Beck, G.A. Gorgone, D. Proud, et al., J. Immunol. 155: 410-418, 1995; and A. Marfaing-Koka, O. Devergne, G. Gorgone, A. Portier, et al., J. Immunol. 154: 1870-1878, 1994), synovial fibroblasts (P. Rathanaswami, M. Hachicha, M. Sadick, T.J. Schall, et al., J. Biol. Chem. 268: 5834-5839, 1993) and dermal fibroblasts (M. Sticherling, M. Kupper, F. Koltrowitz, E. Bornscheuer, et al., J. Invest. Dermatol. 105: 585-591, 1995), mesangial cells (G. Wolf, S. Aberle, F. Thaiss, et al., Kidney Int. 44: 795-804, 1994) and platelets (Y. Koameyoshi, A. Dorschner, A.I. Mallet, E. Christophers, et al., J. Exp. Med. 176: 587-592, 1992). In these cells RANTES mRNA is rapidly upregulated in response to IL-1 or TNF•. Although RANTES mRNA is not usually detected in normal tissues (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995), increased mRNA or protein has been found in diseases characterized by a mononuclear infiltrate. For example, RANTES mRNA was visualized using *in situ* hybridization in renal allografts undergoing rejection (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995; and K.C. Nadeau, H. Azuma and N.I. Tilney, Proc. Natl. Acad. USA 92: 8729-8733, 1995) in the skin of atopic dermatitis patients after exposure to antigen (S. Ying, L. Taborda-Barata, Q. Meng, M. Humbert, et al., J. Exp. Med. 181: 2153-2159, 1995), and in endothelial cells of coronary arteries undergoing accelerated atherosclerosis after cardiac transplant (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995). Further, increased immunoreactive protein for RANTES has been detected in bronchoalveolar lavage fluid (R. Alam, J. York, M. Boyers, et al., Am. J. Resp. Crit. Care Med. 149: A951, 1994) and sputum from asthmatic individuals (C.M. Gelder, P.S. Thomas, D.H. Yates, I.M. Adcock, et al., Thorax 50: 1033-1037, 1995).

Several receptors have been identified that bind RANTES. In particular, CCR5, when expressed in either HEK 293 cells or CHO cells, binds RANTES. This receptor is expressed in T-cells and in monocytes and macrophages, immune/inflammatory cells which are important in the maintenance of a chronic inflammatory reaction. Pharmacological characterization of CCR5 indicates similarities to the RANTES binding site observed on isolated T cells. Therefore, antagonism of RANTES' action on CCR5, as well as antagonism of other natural modulators of CCR5, should inhibit the recruitment and activation of T cells and macrophages into inflammatory lesions and provide a novel therapeutic approach for the treatment of atopic and autoimmune disorders.

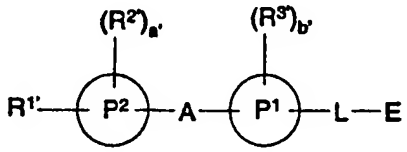
Since T cells and macrophages express CCR5, selective receptor modulators of CCR5, particularly antagonists, are likely to provide beneficial effects in diseases including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases,

atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease, all in mammals, preferably humans. Furthermore, since CD8+ T cells and macrophages have been implicated in COPD, CCR5 may play a role in their recruitment and therefore antagonists to CCR5 could provide potential therapeutic in the treatment of COPD. Also, since CCR5 is a co-receptor for the entry of HIV into cells, selective receptor modulators may be useful in the treatment of HIV infection.

Surprisingly, it has now been discovered that this class of non-peptide compounds, in particular substituted anilide compounds of this invention, function as CCR5 receptor modulators, and therefore, have utility in the treatment and prevention of disease states mediated by CCR5 receptor mechanisms.

## SUMMARY OF THE INVENTION

In one aspect, the present invention is to novel compounds of formula (I), or pharmaceutically active salts thereof, and their novel use in treating the above-mentioned CCR5-mediated disease states:




Formula I

wherein:

the basic nitrogen in moiety E may be optionally quaternized with $C_{1-6}$alkyl or is optionally present as the N-oxide;

$P^1$ and $P^2$ are independently phenyl, fused bicyclic aryl, a monocyclic heterocyclic ring of 5- to 7-members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, or a fused bicyclic heterocyclic ring of 8 to 11-members containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

A is $C(R^{4'})_2$, $CR^{4'}(OR^{5'})$, CO, $C{=}NOR^{6'}$, $NR^{7'}$, oxygen, or $S(O)_{c'}$;

L is a group of formula $-C(=V)-DR^{8'}-$, $-DR^{9'}-C(=V)-$, $-CH_2NH-$, or $-NHCH_2-$;

V is oxygen or sulfur;

D is nitrogen, carbon, or a CH group,

$R^{1'}$ and $R^{2'}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkenyl, aryl, $(CH_2)_{d'}NR^{10'}R^{11'}$, $(CH_2)_{d'}NR^{10'}COR^{12'}$, $(CH_2)_{d'}NR^{10'}CO_2R^{13'}$, $(CH_2)_{d'}NR^{10'}SO_2R^{14'}$,

$(CH_2)_d$CONR$^{15'}$R$^{16'}$, hydroxy$C_{1-6}$alkyl, $C_{1-4}$alkoxyalkyl (optionally substituted by a $C_{1-4}$alkoxy or hydroxy group), $(CH_2)_d$CO$_2$$C_{1-6}$alkyl, $(CH_2)_e$OC(O)R$^{17'}$, CR$^{18'}$=NOR$^{19'}$, CNR$^{20'}$=NOR$^{19'}$, COR$^{21'}$, CONR$^{15'}$R$^{16'}$, CONR$^{15'}$$(CH_2)_f$O$C_{1-4}$alkyl, CONR$^{15'}$$(CH_2)_d$CO$_2$R$^{22'}$, CONHNR$^{23'}$R$^{24'}$, CONR$^{15'}$SO$_2$R$^{25'}$, CO$_2$R$^{26'}$, cyano, trifluoromethyl, NR$^{10'}$R$^{11'}$, NR$^{10'}$COR$^{12'}$, NR$^{27'}$CO$(CH_2)_d$NR$^{27'}$R$^{28'}$, NR$^{27'}$CONR$^{27'}$R$^{28'}$, NR$^{10'}$CO$_2$R$^{13'}$, NR$^{10'}$SO$_2$R$^{14'}$, N=CNR$^{27'}$NR$^{27'}$R$^{28'}$, nitro, hydroxy, $C_{1-6}$alkoxy, hydroxy$C_{1-6}$alkoxy, $C_{1-6}$alkoxy$C_{1-6}$alkoxy, OC(O)NR$^{29'}$R$^{30'}$, SR$^{31'}$, SOR$^{32'}$, SO$_2$R$^{32'}$, SO$_2$NR$^{33'}$R$^{34'}$, halogen, $C_{1-6}$alkanoyl, CO$_2$$(CH_2)_d$OR$^{35'}$, or R$^{1'}$ is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;

R$^{3'}$ is hydrogen, $C_{1-6}$alkyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkenyl, hydroxy$C_{1-6}$alkyl, $C_{1-6}$alkyl$OC_{1-6}$alkyl, CONR$^{36'}$R$^{37'}$, CO$_2$R$^{38'}$, cyano, aryl, trifluoromethyl, NR$^{39'}$R$^{40'}$, nitro, hydroxy, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, acyloxy, or halogen;

R$^{4'}$, R$^{5'}$, R$^{6'}$, R$^{7'}$, R$^{18'}$, R$^{19'}$, R$^{20'}$, R$^{21'}$, R$^{22'}$, R$^{23'}$, R$^{24'}$, R$^{27'}$, R$^{28'}$, R$^{31'}$, R$^{35'}$, R$^{36'}$, R$^{37'}$, R$^{38'}$, R$^{39'}$, and R$^{40'}$ are independently hydrogen or $C_{1-6}$alkyl;

R$^{8'}$ is hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group;

R$^{9'}$ is hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group;

R$^{10'}$ and R$^{11'}$ are independently hydrogen or $C_{1-6}$alkyl, or R$^{10'}$ and R$^{11'}$ together with the nitrogen to which they are attached, forms a 5- to 6-membered heterocyclic ring, which may optionally be substituted by an oxo group, and, when there are six members, may optionally contain in the ring one oxygen or one sulfur atom;

R$^{12'}$ is hydrogen, $C_{1-6}$alkyl, or $C_{1-4}$alkoxyalkyl;

R$^{13'}$, R$^{25'}$, and R$^{32'}$ are independently $C_{1-6}$alkyl;

R$^{14'}$ is $C_{1-6}$alkyl or phenyl;

R$^{15'}$ and R$^{16'}$ are independently hydrogen or $C_{1-6}$alkyl, or R$^{15'}$ and R$^{16'}$ together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when there are 6 ring members, may optionally contain in the ring one oxygen or one sulfur atom;

R$^{17'}$ is $C^{1-4}$alkyl, optionally substituted by $C_{1-6}$alkoxy;

R$^{26'}$ is hydrogen or $C_{1-6}$alkyl optionally substituted with one or two substituents selected from $C_{1-6}$alkyl, $C_{1-6}$alkoxy, hydroxy, or NR$^{10'}$R$^{11'}$;

R$^{29'}$ and R$^{30'}$ are independently hydrogen or $C_{1-6}$alkyl, or R$^{29'}$ and R$^{30'}$ together with the nitrogen to which they are attached form a 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or sulfur atom;

$R^{33'}$ and $R^{34'}$ are independently hydrogen or $C_{1-6}$alkyl, or $R^{33'}$ and $R^{34'}$ together with the nitrogen to which they are attached form 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or one sulfur atom;

a' and b' are independently 1, 2, or 3;

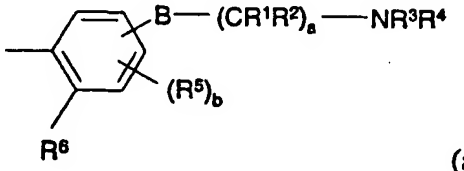
c' is 0, 1, or 2;

d' is 1, 2, 3, or 4;

e' is 0, 1, 2, or 3;

f' is 1, 2, or 3;

E represents (a):




(a);

in which

B is oxygen, $S(O)_c$, $CR^7{=}CR^8$, or $CR^7R^8$, or B is $NR^9$;

$R^1$ and $R^2$ are independently hydrogen or $C_{1-6}$alkyl; alternatively $B(CR^1R^2)_a$ is $OCR^1R^2CR^1(OH)CR^1R^2$ or $OCR^1R^2CR^1(OCOCH_3)CR^1R^2$;

$R^3$ and $R^4$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, hydroxy, $OCOR^{12}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{13}$, and $NHCO_2R^{14}$;

$R^5$ is hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{15}R^{16}$, $CO_2R^{17}$, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$ or halogen;

$R^6$ is hydrogen, $C_{1-6}$alkyl, aryl, trifluoromethyl, hydroxy, $C_{1-6}$alkoxy or halogen, or $R^6$ taken together with $R^{8'}$ forms a group D where D is $(CR^{22}R^{23})_e$ or D is $(CR^{22}R^{23})_f$-G where G is oxygen, sulfur or $CR^{22}{=}CR^{23}$, $CR^{22}{=}N$, $=CR^{22}O$, $=CR^{22}S$, or $=CR^{22}{-}NR^{23}$;

$R^7$, $R^8$, $R^{10}$, $R^{11}$, $R^{12}$, $R^{15}$, $R^{16}$, $R^{17}$, $R^{20}$, $R^{21}$, $R^{22}$, and $R^{23}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^9$ is hydrogen, $C_{1-6}$alkyl, or phenyl$C_{1-6}$alkyl;

$R^{13}$, $R^{14}$, $R^{18}$, and $R^{19}$ are independently $C_{1-6}$alkyl;

a is 1, 2, 3, or 4;

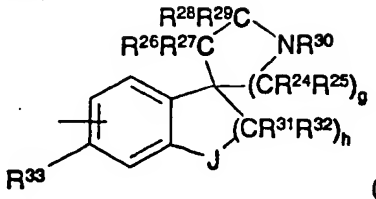
b is 1 or 2;

c and d are independently 0, 1 or 2;

e is 2, 3 or 4;

f is 0, 1, 2 or 3;

alternatively, E represents (b):



(b);

$R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{31}$, and $R^{32}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{30}$ is hydrogen, $C_{1-6}$alkyl, or $C_{3-7}$cycloalkyl;

$R^{33}$ is hydrogen, $C_{1-6}$alkyl, trifluoromethyl, hydroxy, or halogen, or $R^{33}$ and $R^{8'}$ together form a group -K- where K is $(CR^{34}R^{35})_i$ or K is $(CR^{34}R^{35})_j$ -M and M is oxygen, sulfur, $CR^{34}=CR^{35}$, $CR^{34}=N$, or N=N;

J is oxygen, $CR^{36}R^{37}$, or $NR^{38}$, or J is a group $S(O)_k$;

$R^{34}$, $R^{35}$, $R^{36}$, $R^{37}$, and $R^{38}$ are independently hydrogen or $C_{1-6}$alkyl;

g is 1, 2 or 3;

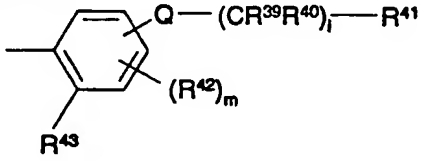
h is 1, 2 or 3;

i is 2, 3, or 4;

j is 0, 1, 2, or 3;

k is 0, 1 or 2;

alternatively, E represents (c):



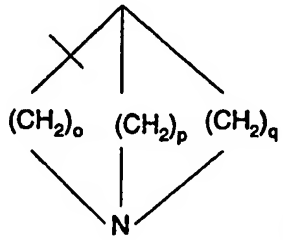
(c);

in which:

Q is oxygen, $S(O)_n$, $CR^{44}=CR^{45}$, $CR^{44}R^{45}$, or Q is $NR^{46}$;

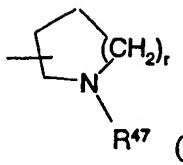
$R^{39}$ and $R^{40}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{41}$ is a group of formula (d):



(d)

or $R^{41}$ is a group of formula (e):



(e)

$R^{42}$ is hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{48}R^{49}$, $CO_2R^{50}$, trifluoromethyl, $NHCO_2R^{51}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_sR^{52}$, $SO_2NR^{53}R^{54}$, or halogen;

$R^{43}$ is hydrogen or $R^{43}$ together with $R^{8'}$ forms a group R where R is $CR^{55}=CR^{56}$, $CR^{55}=CR^{56}CR^{55}R^{56}$, or $(CR^{55}R^{56})t$;

$R^{44}$, $R^{45}$, $R^{46}$, $R^{48}$, $R^{49}$, $R^{50}$, $R^{53}$, $R^{54}$, $R^{55}$, and $R^{56}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{47}$ is hydrogen, $C_{1-6}$alkyl, or $C_{3-7}$ cycloalkyl;

$R^{51}$ and $R^{52}$ are independently $C_{1-6}$alkyl;

l is 0, 1, 2, or 3;

m is 1 or 2;

n is 0, 1, or 2

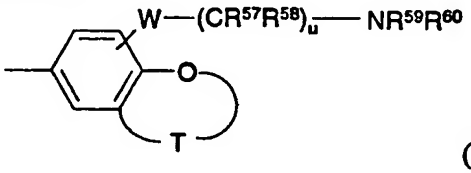
o, p, and q are independently integers having the value 1, 2, or 3;

r is 0,1, 2, or 3;

s is 0, 1, or 2;

t is 2 or 3;

alternatively, E represents (f):



(f);

$R^{57}$ and $R^{58}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{59}$ and $R^{60}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{61}R^{62}$, $NR^{61}R^{62}$, hydroxy, $OCOR^{63}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{64}$, and $NHCO_2R^{65}$;

T is $-(CR^{66}R^{67})_v-$ or $-O(CR^{66}R^{67})_w-$;

W is oxygen, $S(O)_x$, $NR^{68}$, or W is $CR^{69}=CR^{70}$ or $CR^{69}R^{70}$;

$R^{61}$, $R^{62}$, $R^{63}$, $R^{66}$, $R^{67}$ $R^{68}$, $R^{69}$, and $R^{70}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{64}$ and $R^{65}$ are independently $C_{1-6}$alkyl;

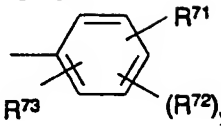
u is 1 to 4;

v is 2 or 3;

w is 1, 2, or 3;

x is 0, 1 or 2;

alternatively, E represents a group (g):



(g);

$R^{71}$ is an optionally substituted 5 to 7-membered saturated or partially saturated heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur or $R^{71}$ is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom and optionally a further heteroatom selected from oxygen, nitrogen or sulfur;

$R^{72}$ is hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{74}R^{75}$, $CO_2R^{76}$, trifluoromethyl, $NHCO_2R^{77}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_zR^{78}$, $SO_2NR^{79}R^{80}$, or halogen;

$R^{73}$ is hydrogen, $C_{1-6}$alkyl, hydroxy, $C_{1-6}$alkoxy or halogen, or $R^{73}$ and $R^{8'}$ taken together from a group -X- where X is $(CR^{81}R^{82})_{aa}$ or X is $(CR^{81}R^{82})_{ab}$-Y and Y is oxygen, sulfur or $CR^{81}=CR^{82}$;

$R^{74}$, $R^{75}$, $R^{76}$, $R^{79}$, $R^{80}$, $R^{81}$, and $R^{82}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{77}$ and $R^{78}$are independently $C_{1-6}$alkyl;

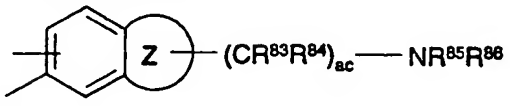
y is 1 or 2;

z is 0, 1, or 2;

aa is 2, 3 or 4;

ab is 0, 1, 2 or 3;

alternatively, E represents group (h):



(h);

$R^{83}$ and $R^{84}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{85}$ and $R^{86}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{88}R^{89}$, $NR^{90}R^{91}$, hydroxy, $OCOR^{92}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{93}$, and $NHCO_2R^{94}$;

$R^{87}$ is hydrogen or $C_{1-6}$alkyl, $C_{1-6}$alkoxy, or halogen, or $R^{87}$ together with $R^{8'}$ forms a group -AA- where AA is $(CR^{95}R^{96})_{ad}$ or AA is $(CR^{95}=CR^{96})_{ae}$-AB and AB is oxygen, sulfur, $CR^{95}=CR^{96}$, $CR^{95}=N$, $CR^{95}NR^{96}$ or N=N;

Z is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

$R^{88}$, $R^{89}$, $R^{90}$, $R^{91}$, $R^{92}$, $R^{95}$, and $R^{96}$ are independently hydrogen or $C_{1-6}$alkyl;

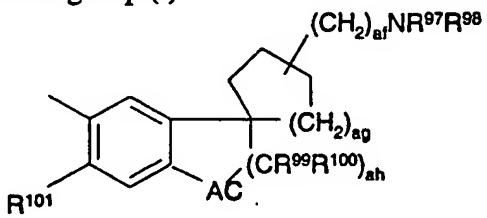
$R^{93}$ and $R^{94}$ are independently $C_{1-6}$alkyl;

ac is 0 to 4;

ad is 1, 2 or 3;

ae is 0, 1 or 2;

alternatively, E represents group (i):




(i);

$R^{97}$ and $R^{98}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{102}R^{103}$, $NR^{104}R^{105}$, hydroxy, $OCOR^{106}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{107}$, and $NHCO_2R^{108}$;

$R^{99}$ and $R^{100}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{101}$ is hydrogen or $C_{1-6}$alkyl or $R^{101}$ and $R^{8'}$ together form a group -AD- where AD is $(CR^{109}R^{110})$ai or AD is $(CR^{109}R^{110})_{aj}$-AE and AE is oxygen, sulfur or $CR^{109}=CR^{110}$;

AC is oxygen, $CR^{111}R^{112}$ or $NR^{113}$ or AC is a group $S(O)_{ak}$;

$R^{102}$, $R^{103}$, $R^{104}$, $R^{105}$, $R^{106}$, $R^{109}$, $R^{110}$, $R^{111}$, $R^{112}$, and $R^{113}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{107}$ and $R^{108}$ are independently $C_{1-6}$alkyl;

af is 0, 1, 2, 3, or 4;

ag is 1, 2, or 3;

ah is 1, 2, 3 or 4;

ai is 2, 3 or 4;

aj is 0, 1, 2, or 3; and

ak is 0, 1 or 2.

In another aspect, the present invention is to a method of treating CCR5 mediated disease states, including, but not limited to, COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic disease, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease and HIV infection, all in mammals, preferably humans, comprising administering to such mammal in need thereof, a anilide of formula (I), or pharmaceutically active salts thereof.

In yet another aspect, the present invention is to pharmaceutical compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier therefor. In particular, the pharmaceutical compositions of the present invention are used for treating CCR5-mediated disease states, including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic disease, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, COPD and HIV all in mammals, preferably humans.

DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that substituted anilides of formula (I) are CCR5 receptor modulators. It has also now been discovered that selective inhibition of CCR5 receptor mechanisms by treatment with the receptor modulators of formula (I), or a pharmaceutically acceptable salt thereof, represents a novel therapeutic and preventative approach to the treatment of a variety of disease states, including, but not limited to, COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic disease, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease, all in mammals, preferably humans ("CCR5-mediated diseases"). Also, since CCR5 is a co-receptor for the entry of HIV into cells, selective receptor modulators may be useful in the treatment of HIV infection.

The term "alkyl" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

The terms "cycloalkyl" and "cyclic alkyl" are used herein at all occurrences to mean cyclic radicals, preferably comprising 3 to 7 carbon atoms which may be mono- or bicyclo-fused ring systems which may additionally include unsaturation, including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, and the like.

The terms "halo" or "halogen" are used interchangeably herein at all occurrences to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The term "heterocyclic ring" is used herein at all occurrences to mean a saturated or partially saturated 5-, 6-, or 7-membered ring system (unless the cyclic ring system is otherwise limited) in which the ring system contains one to 3 heteroatoms selected from oxygen, sulfur, or nitrogen, which ring system may be optionally substituted with $C_{1-6}$alkyl or $C_{3-7}$cycloalkyl. Examples of such rings include, but are not limited to, piperidine, tetrahydropyridine, and piperazine. When the heterocyclic ring is fused to a phenyl group, the term "heterocyclic ring", together with the phenyl ring to which it is fused, forms a ring which includes, but is not limited to, dihydro-1,4-benzoxazine and 1,2,3,4-tetrahydroquinoline, which may be optionally substituted by $C_{1-6}$alkyl or oxo.

The term "6,6 or 6,5 bicyclic ring" means a 6,6 or 6,5-bicyclic ring system containing a nitrogen atom and optionally a further heteroatom selected from nitrogen, oxygen, or sulfur, which ring system may be optionally substituted with $C_{1-6}$alkyl. Examples of such ring systems include, but are not limited to, tropane, isoquinuclidine and granatane rings.

The term "CCR5 mediated disease state" is used herein at all occurrences to mean any disease state which is mediated (or modulated) by CCR5.

The term "monocyclic heterocyclic ring" is used herein at all occurrences to mean a single aromatic ring of 5 to 7 members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur represented by $P^1$ and/or $P^2$ including thienyl, furyl, pyrrolyl, and pyridyl.

The term "fused bicyclic heterocyclic ring" is used herein at all occurrences to mean a fused bicyclic ring system of 8 to 11 members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur including indole, benzofuran, benzothiophene, quinoline, and isoquinoline rings.

Suitably, pharmaceutically acceptable salts of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate, or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate, and stearate.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like, are equivalent to the unsolvated forms for purposes of this invention.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. The stereocenters may be of any combination of R and S configuration, for example, (R,R), (R,S), (S,S) or (S,R). All of these compounds are within the scope of the present invention.

For the compounds of formula (I) various embodiments are as follows. It will be understood that the basic nitrogen in moiety E may be optionally quaternized with $C_{1-6}$alkyl or is optionally present as the N-oxide.

$P^1$ and $P^2$ are suitably independently phenyl, fused bicyclic aryl, a monocyclic heterocyclic ring of 5- to 7-members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, or a fused bicyclic heterocyclic ring of 8 to 11-members containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur. Preferably, $P^1$ is phenyl and $P^2$ is phenl or quinoxalinyl. More preferably $P^1$ and $P^2$ are phenyl.

When $R^{1'}$ is a 5- to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen, or sulfur, suitable heterocyclic rings include aromatic groups such as thienyl, furyl, pyrrolyl, triazolyl, diazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, and dioxanyl. Saturated and partially saturated rings are also within the scope of the invention, in particular rings including an oxo or thioxo moiety such as lactams and thiolactams. Suitably, the heterocyclic ring can be linked to the remainder of the molecule via a carbon atom, or, when present, a nitrogen atom. Suitable substituents for these rings include one to two of $R^{3'}$.

A is $C(R^{4'})_2$, $CR^{4'}(OR^{5'})$, CO, $C{=}NOR^{6'}$, $NR^{7'}$, oxygen, or $S(O)_{c'}$. Preferably A is $C(R^{4'})_2$, CO, $C{=}NOR^{6'}$, $NR^{7'}$, oxygen, or sulfur. More preferably, A is $CH_2$, CO, C=NOH, oxygen or sulfur. Most preferably, A is $CH_2$, CO, oxygen or sulfur. Preferably, A is attached to $P^1$ meta or para to L, more preferably, A is attached to $P^1$ para to L.

L is suitably a group of formula $-C(=V)-DR^{8'}-$, $-DR^{9'}-C(=V)-$, $-CH_2NH-$, or $-NHCH_2-$. L is preferably $-C(=V)-DR^{8'}-$.

V is suitably oxygen or sulfur. V is preferably oxygen.

D is suitably nitrogen, carbon or a CH group. D is preferably nitrogen.

$R^{1'}$ and $R^{2'}$ are suitably independently hydrogen, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkenyl, aryl, $(CH_2)_{d'}NR^{10'}R^{11'}$, $(CH_2)_{d'}NR^{10'}COR^{12'}$, $(CH_2)_{d'}NR^{10'}CO_2R^{13'}$, $(CH_2)_{d'}NR^{10'}SO_2R^{14'}$, $(CH_2)_{d'}CONR^{15'}R^{16'}$, hydroxy$C_{1-6}$alkyl, $C_{1-4}$alkoxyalkyl (optionally substituted by a $C_{1-4}$alkoxy or hydroxy group), $(CH_2)_{d'}CO_2C_{1-6}$alkyl, $(CH_2)_{e'}OC(O)R^{17'}$, $CR^{18'}{=}NOR^{19'}$, $CNR^{20'}{=}NOR^{19'}$, $COR^{21'}$, $CONR^{15'}R^{16'}$, $CONR^{15'}(CH_2)_fOC_{1-4}$alkyl, $CONR^{15'}(CH_2)_{d'}CO_2R^{22'}$, $CONHNR^{23'}R^{24'}$, $CONR^{15'}SO_2R^{25'}$, $CO_2R^{26'}$, cyano, trifluoromethyl, $NR^{10'}R^{11'}$, $NR^{10'}COR^{12'}$, $NR^{27'}CO(CH_2)_{d'}NR^{27'}R^{28'}$, $NR^{27'}CONR^{27'}R^{28'}$, $NR^{10'}CO_2R^{13'}$, $NR^{10'}SO_2R^{14'}$, $N{=}CNR^{27'}NR^{27'}R^{28'}$, nitro, hydroxy, $C_{1-6}$alkoxy, hydroxy$C_{1-6}$alkoxy, $C_{1-6}$alkoxy$C_{1-6}$alkoxy, $OC(O)NR^{29'}R^{30'}$, $SR^{31'}$, $SOR^{32'}$, $SO_2R^{32'}$,

$SO_2NR^{33'}R^{34'}$, halogen, $C_{1-6}$alkanoyl, $CO_2(CH_2)_dOR^{35'}$, or $R^{1'}$ is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur. $R^{1'}$ and $R^{2'}$ are preferably hydrogen, $C_{1-6}$alkyl, hydroxy, or halogen.

$R^{3'}$ is suitably hydrogen, $C_{1-6}$alkyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkenyl, hydroxy$C_{1-6}$alkyl, $C_{1-6}$alkyl$OC_{1-6}$alkyl, $CONR^{36'}R^{37'}$, $CO_2R^{38'}$, cyano, aryl, trifluoromethyl, $NR^{39'}R^{40'}$, nitro, hydroxy, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, acyloxy, or halogen. $R^{3'}$ is preferably hydrogen, nitro, sulfamoyl or $C_{1-6}$alkylamino.

$R^{4'}$, $R^{5'}$, $R^{6'}$, $R^{7'}$, $R^{18'}$, $R^{19'}$, $R^{20'}$, $R^{21'}$, $R^{22'}$, $R^{23'}$, $R^{24'}$, $R^{27'}$, $R^{28'}$, $R^{31'}$, $R^{35'}$, $R^{36'}$, $R^{37'}$, $R^{38'}$, $R^{39'}$, and $R^{40'}$ are suitably independently hydrogen or $C_{1-6}$alkyl;

$R^{8'}$ is suitably hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group. $R^{8'}$ is preferably hydrogen.

$R^{9'}$ is suitably hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group.

$R^{10'}$ and $R^{11'}$ are suitably independently hydrogen or $C_{1-6}$alkyl, or $R^{10'}$ and $R^{11'}$ together with the nitrogen to which they are attached, forms a 5- to 6-membered heterocyclic ring, which may optionally be substituted by an oxo group, and, when there are six members, may optionally contain in the ring one oxygen or one sulfur atom.

$R^{12'}$ is suitably hydrogen, $C_{1-6}$alkyl, or $C_{1-4}$alkoxyalkyl.

$R^{13'}$, $R^{25'}$, and $R^{32'}$ are suitably independently $C_{1-6}$alkyl.

$R^{14'}$ is suitably $C_{1-6}$alkyl or phenyl.

$R^{15'}$ and $R^{16'}$ are suitably independently hydrogen or $C_{1-6}$alkyl, or $R^{15'}$ and $R^{16'}$ together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when there are 6 ring members, may optionally contain in the ring one oxygen or one sulfur atom.

$R^{17'}$ is suitably $C^{1-4}$alkyl, optionally substituted by $C_{1-6}$alkoxy.

$R^{26'}$ is suitably hydrogen or $C_{1-6}$alkyl optionally substituted with one or two substituents selected from $C_{1-6}$alkyl, $C_{1-6}$alkoxy, hydroxy, or $NR^{10'}R^{11'}$.

$R^{29'}$ and $R^{30'}$ are suitably independently hydrogen or $C_{1-6}$alkyl, or $R^{29'}$ and $R^{30'}$ together with the nitrogen to which they are attached form a 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or sulfur atom.

$R^{33'}$ and $R^{34'}$ are suitably independently hydrogen or $C_{1-6}$alkyl, or $R^{33'}$ and $R^{34'}$ together with the nitrogen to which they are attached form 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or sulfur atom.

a' and b' are independently 1, 2, or 3.

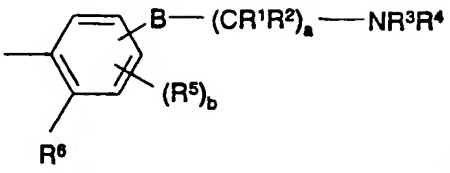
c' is suitably 0, 1, or 2.

d' is suitably 1, 2, 3, or 4.

e' is suitably 0, 1, 2, or 3.

f' is suitably 1, 2, or 3.

E suitably represents (a):




(a);

in which

B is suitably oxygen, $S(O)_c$, $CR^7{=}CR^8$, or $CR^7R^8$, or B is $NR^9$. B is preferably $CR^7R^8$, or oxygen. More preferably, B is $CH_2$ or oxygen.

$R^1$ and $R^2$ are suitably independently hydrogen or $C_{1-6}$alkyl; alternatively $B(CR^1R^2)_a$ is $OCR^1R^2CR^1(OH)CR^1R^2$ or $OCR^1R^2CR^1(OCOCH_3)CR^1R^2$. Preferably, $R^1$ and $R^2$ are hydrogen.

$R^3$ and $R^4$ are suitably independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, hydroxy, $OCOR^{12}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{13}$, and $NHCO_2R^{14}$. Preferably $R^3$ and $R^4$ are both $C_{1-6}$alkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur. More preferably, $R^3$ and $R^4$ are $C_{3-6}$alkyl, or together with the nitrogen to which they are attached form a 6-membered ring, optionally substituted with one or more of $C_{1-6}$alkyl, N-acetamido, or hydroxy. Most preferably, $R^3$ and $R^4$ are isopropyl or $R^3$ is isopropyl and $R^4$ is tert-butyl, or together with the nitrogen to which they are attached are 1-(2,2,6,6-tetramethylpiperidinyl), 1-(4-acetamido-2,2,6,6-tetramethylpiperidinyl), 1-(4-hydroxy-2,2,6,6-tetramethylpiperidinyl), or 1-(4-hydroxy-2,2,4,6,6-pentamethylpiperidinyl).

Preferably, $B\text{-}(CR^1R^2)_a\text{-}NR^3R^4$ is ortho to $R^5$, meta to L, and para to $R^6$, and $R^5$ is para to L.

$R^5$ is suitably hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{15}R^{16}$, $CO_2R^{17}$, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$, or halogen. $R^5$ is preferably $C_{1-6}$alkoxy,

$SC_{1-6}$alkyl, or halogen; more preferably methoxy, methylthio, or iodo, most preferably methoxy. When $R^5$ is methoxy, it is preferably para to L.

$R^6$ is suitably hydrogen, $C_{1-6}$alkyl, aryl, trifluoromethyl, hydroxy, $C_{1-6}$alkoxy, or halogen, or $R^6$ taken together with $R^{8'}$ forms a group D where D is $(CR^{22}R^{23})_e$ or D is $(CR^{22}R^{23})_f$-G where G is oxygen, sulfur, or $CR^{22}=CR^{23}$, $CR^{22}=N$, $=CR^{22}O$, $=CR^{22}S$, or $=CR^{22}$-$NR^{23}$. Preferably, $R^6$ is hydrogen.

$R^7$, $R^8$, $R^{10}$, $R^{11}$, $R^{15}$, $R^{16}$, $R^{17}$, $R^{20}$, $R^{21}$, $R^{22}$, and $R^{23}$ are independently hydrogen or $C_{1-6}$alkyl.

$R^9$ is hydrogen, $C_{1-6}$alkyl, or phenyl$C_{1-6}$alkyl.

$R^{12}$, $R^{13}$, $R^{14}$, $R^{18}$, and $R^{19}$ are independently $C_{1-6}$alkyl.

a is suitably 1, 2, 3, or 4. Preferably, a is 2 or 3, more preferably, a is 2 or 3 when B is oxygen and a is 2 when B is $CH_2$, most preferably, a is 2 when B is oxygen.

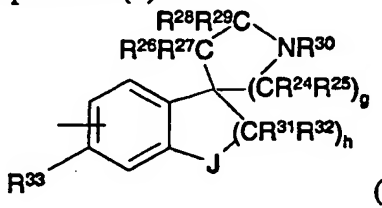
b is suitably 1 or 2. Preferably, b is 1.

c and d are suitably independently 0, 1, or 2.

e is suitably 2, 3, or 4.

f is suitably 0, 1, 2, or 3.

alternatively, E suitably represents (b):




(b);

$R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{31}$, and $R^{32}$ are suitably independently hydrogen or $C_{1-6}$alkyl. $R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{31}$, and $R^{32}$ are preferably hydrogen.

$R^{30}$ is suitably hydrogen, $C_{1-6}$alkyl, or $C_{3-7}$cycloalkyl. Preferably, $R^{30}$ is $C_{1-6}$alkyl, more preferably, $R^{30}$ is $C_{3-6}$alkyl, most preferably, $R^{30}$ is isopropyl.

$R^{33}$ is suitably hydrogen, $C_{1-6}$alkyl, trifluoromethyl, hydroxy, or halogen, or $R^{33}$ and $R^{8'}$ together form a group -K- where K is $(CR^{34}R^{35})_i$ or K is $(CR^{34}R^{35})_j$ -M and M is oxygen, sulfur, $CR^{34}=CR^{35}$, $CR^{34}=N$, or N=N. Preferably, $R^{33}$ is hydrogen.

J is suitably oxygen, $CR^{36}R^{37}$, or $NR^{38}$, or J is a group $S(O)_k$, Preferably, J is oxygen. Preferably, J is para to L.

$R^{34}$, $R^{35}$, $R^{36}$, $R^{37}$, $R^{38}$ are suitably independently hydrogen or $C_{1-6}$alkyl.

g is suitably 1, 2, or 3. Preferably, g is 2 or 3, more preferably 2.

h is suitably 1, 2, or 3. Preferably, h is 1.

i is suitably 2, 3, or 4.

j is suitably 0, 1, 2, or 3.

k is suitably 0, 1 or 2.

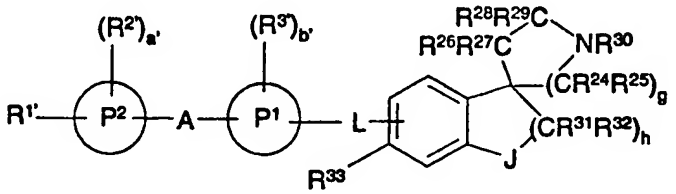
Known compounds overlapping with the scope of the instant invention are as follows.

A subgenus of formula (I) wherein: the basic nitrogen in moiety E may be optionally quaternized with $C_{1-6}$alkyl or is optionally present as the N-oxide; E is (b); J is $CH_2$; g is 1, 2, or 3; h is 1, 2, or 3; $R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{31}$, and $R^{32}$ are hydrogen; $R^{30}$ is hydrogen or $C_{1-6}$alkyl; $R^{33}$ is hydrogen, $C_{1-6}$alkyl, trifluoromethyl, or halogen; L is $CONR^{8'}$ or $NR^{9'}CO$; $R^{8'}$ and $R^{9'}$ are independently hydrogen or $C_{1-6}$alkyl; $P^1$ and $P^2$ are phenyl; A is CO, O or $S(O)_{0-2}$; $R^{1'}$ is hydrogen; $R^{2'}$ is hydrogen or 1, 2, or 3 of hydroxy, $C_{1-3}$alkyl, cyano, halogen, or trifluoromethyl; $R^{3'}$ is hydrogen or 1 or 2 of hydroxy, cyano, halogen, trifluoromethyl, $CONR^{36*}R^{37*}$, $COC_{1-5}$alkyl, $CO_2R^{38*}$, $C_{1-6}$alkoxy, or phenyl; and $R^{36*}$, $R^{37*}$, and $R^{38*}$ are independently hydrogen or $C_{1-6}$alkyl, has been described in WO 98/25604, published 18 June 1998, as chemokine receptor modulators.

Further, a subgenus of formula (I) wherein: the basic nitrogen in moiety E may be optionally quaternized with $C_{1-6}$alkyl or is optionally present as the N-oxide; E is (b); J is $CH_2$; g is 1, 2, or 3; h is 1, 2, or 3; $R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{31}$, and $R^{32}$ are hydrogen; $R^{30}$ is hydrogen or $C_{1-6}$alkyl; $R^{33}$ is hydrogen, $C_{1-6}$alkyl, trifluoromethyl, or halogen; L is $CH_2NH$; $P^1$ is heteroaryl, wherein heteroaryl is selected from the group consisting of benzimidazolyl, benzofuranyl, benzooxazolyl, furanyl, imidazolyl, indolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolyl, quinolyl, thiadiazolyl, thiazolyl, thienyl or triazolyl; A is CO, O or $S(O)_{0-2}$; $P^2$ is phenyl; $R^{1*}$ is hydrogen or one of hydroxy, cyano, halogen, trifluoromethyl, $NR^{10*}COR^{12*}$, $NR^{10*}CO_2R^{13*}$, $NR^{27*}CONHR^{28*}$, $NHS(O)_{0-2}R^{14*}$, $CONR^{15*}R^{16*}$, $COC_{1-5}$alkyl, $CO_2R^{26*}$, $C_{1-6}$alkoxy, $SR^{31*}$, $SOR^{32*}$, $SO_2R^{32*}$, or phenyl, or $R^{1*}$ is an optionally substituted heterocyclic ring selected from furanyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl or triazolyl; $R^{2*}$ is hydrogen or 1, or 2 of hydroxy, cyano, halogen, trifluoromethyl, $NR^{10*}COR^{12*}$, $NR^{10*}CO_2R^{13*}$, $NR^{27*}CONHR^{28*}$, $NHS(O)_{0-2}R^{14*}$, $CONR^{15*}R^{16*}$, $COC_{1-5}$alkyl, $CO_2R^{26*}$, $C_{1-6}$alkoxy, $SR^{31*}$, $SOR^{32*}$, $SO_2R^{32*}$, or phenyl; $R^{3'}$ is hydrogen or 1 or 2 of hydroxy, cyano, halogen, trifluoromethyl, $CONR^{36*}R^{37*}$, $COC_{1-5}$alkyl, $CO_2R^{38*}$, $C_{1-6}$alkoxy, or phenyl; $R^{10*}$, $R^{12*}$, $R^{15*}$, $R^{16*}$, $R^{27*}$, $R^{28*}$, $R^{31*}$, $R^{36*}$, $R^{37*}$, and $R^{38*}$ are independently hydrogen or $C_{1-6}$alkyl; $R^{13*}$ and $R^{32*}$ are independently $C_{1-6}$alkyl; $R^{14*}$ is $C_{1-6}$alkyl or phenyl; and $R^{26*}$ is hydrogen or $C_{1-6}$alkyl optionally substituted with one or two of hydroxy, has been

described in WO 98/25604, published 18 June 1998, as chemokine receptor modulators.

A preferred subgenus of the compounds of formula (I) are compounds of formula (Ia) in which $R^{1'}$, $R^{2'}$, $R^{3'}$, $P^1$, $P^2$, A, a', b', L, $R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{30}$, $R^{31}$, $R^{32}$, $R^{33}$, J, g, and h are defined as above:




Formula (Ia)

Among the preferred compounds of the invention are the following compounds:

N-[4-[2-(Dimethylamino)ethyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl)-4-phenoxybenzamide;

N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]]-4-phenoxybenzamide;

N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-3-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-(phenylmethyl)benzamide;

N-[2-[2-(Diethylamino)ethoxy]phenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2-(phenylmethyl)thiazole-4-carboxamide hydrochloride;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide Methiodide;

N-[1-[2-[Bis(1-methylethyl)amino]ethyl]-1,2,3,4-tetrahydroquinol-7-yl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(3-hydroxyphenoxy)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfinyl]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(2,4-dichlorophenyl)sulfinyl]-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-benzoylbenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(methylphenylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylthio)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfonyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfinyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(hydroxyimino)phenylmethyl]benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(hydroxyphenylmethyl)benzamide;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-benzoylbenzamide trifluoroacetate;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide; and

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide.

Among the more preferred compounds of this invention are the following compounds:

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide methiodide

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)oxy]-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)oxy]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylthio)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(hydroxyimino)phenylmethyl]benzamide;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-benzoylbenzamide trifluoroacetate;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide; and

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide.

Among the most preferred compounds of this invention are the following compounds:

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-benzoylbenzamide trifluoroacetate;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide; and

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide.

Among compounds excluded from this invention are the following compounds:

N-[2-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-phenoxybenzamide;

N-[2-[2-(Diethylamino)ethoxy]phenyl]-4-phenoxybenzamide;

N-[4-[2-(Diethylamino)ethoxy]phenyl]-3-phenoxybenzamide;

N-[2-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-3-phenoxybenzamide ;

N-[2-[2-(Diethylamino)ethoxy]phenyl]-3-phenoxybenzamide;

N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(phenylmethyl)benzamide; and

N-[2-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-(phenylmethyl)benzamide.

**Formulation of Pharmaceutical Compositions**

The pharmaceutically effective compounds of this invention (and the pharmaceutically acceptable salts thereof) are administered in conventional dosage forms prepared by combining a compound of this invention ("active ingredient") in an amount sufficient to treat COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, ("CCR5-mediated disease states") with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or

diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1000 mg. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The active ingredient may also be administered topically to a mammal in need of treatment or prophylaxis of CCR5 mediated disease states. The amount of active ingredient required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the disease state being treated and the mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of the active ingredient externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous or alcoholic solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

The active ingredient may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage amount of the active ingredient administered by inhalation is from about 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

In one aspect, this invention relates to a method of treating COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, all in mammals, preferably humans, which comprises administering to such mammal an effective amount of a CCR5 receptor modulator, in particular, a compound of this invention.

By the term "treating" is meant either prophylactic or therapeutic therapy. Such compound can be administered to such mammal in a conventional dosage form prepared by combining the compound of this invention with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The compound is administered to a mammal in need of treatment for COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic diseases, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, in an amount sufficient to decrease symptoms associated with these disease states. The route of administration may be oral or parenteral.

The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day of active ingredient. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day of active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of this invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

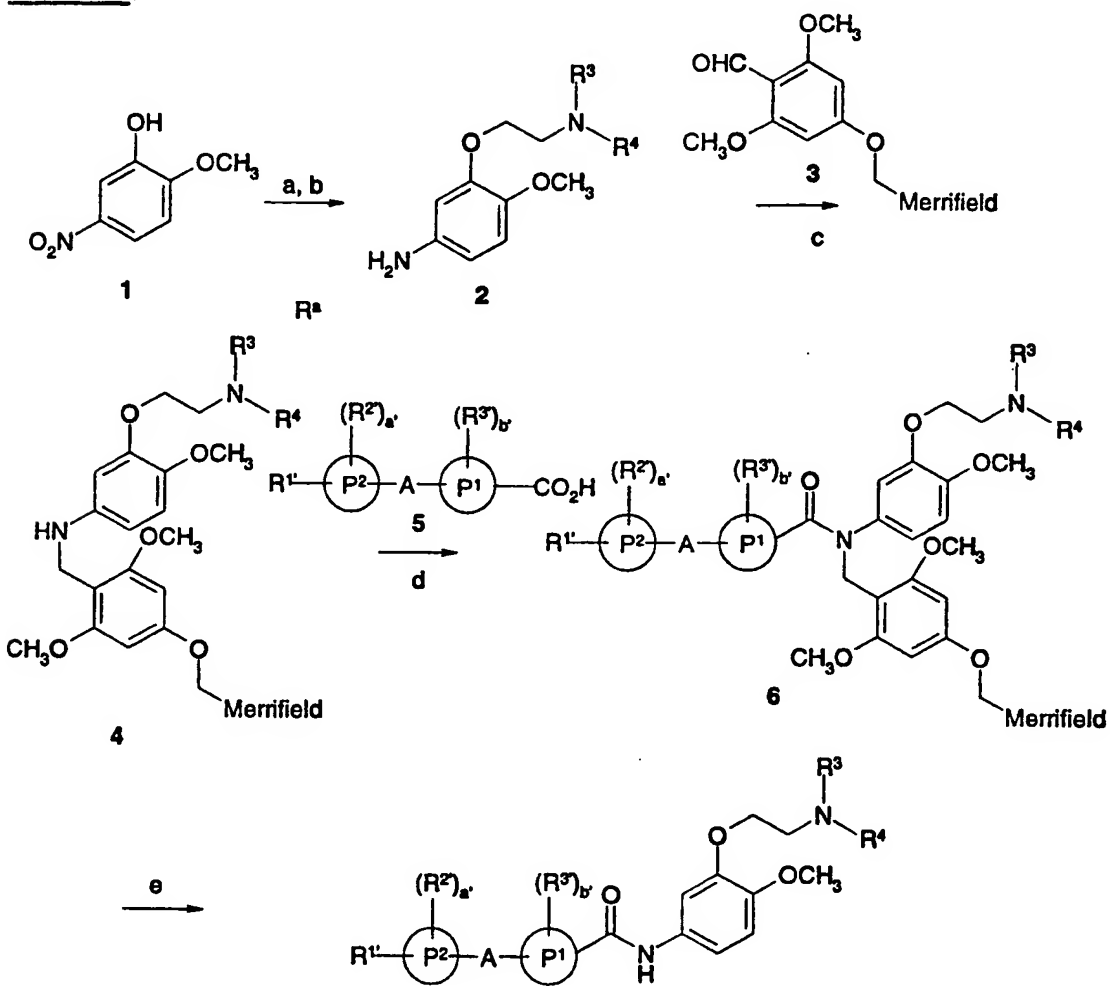
Methods of Preparation

Compounds of formula (I) are prepared by condensing suitably substituted aryl or heteroarylcarboxylic acids and suitably substituted anilines, which are commercially available or synthesized by methods known to the art from commercially available starting materials, using methods known to the art. For example, suitably substituted aryl or heteroarylcarboxylic acids are treated with a suitable reagent, such as thionyl chloride, at a suitable temperature, such as at reflux, to afford aryl or heteroarylcarbonyl chlorides, and the aryl- or heteroarylcarbonyl chlorides are condensed with suitably substituted anilines in the presence of a suitable base, such as diisopropylethylamine, in a suitable solvent, such as dichloromethane, to give compounds of formula (I). Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I-VI (published by Wiley-Interscience).

Compounds of formula (I) are also prepared using solid-phase chemistry as described in Scheme I and using the general method described in international patent application WO 99/01127, published 14 January 1999. For example, in Scheme 1, an appropriately substituted 3-(2-aminoethoxy)-4-methoxyaniline **I-2**, such as 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline, which is synthesized from the commercially available 2-methoxy-5-nitrophenol, **I-1**, according to the procedures described in WO 99/01127, is attached to a polymer support such as Merrifield resin-bound aldehyde **I-3**, which is synthesized according to the general protocol of Boojamra et al., (*J. Org. Chem.*, **1995**, 60, 5742-3) by reductive amination employing a reducing agent such as sodium triacetoxyborohydride in dimethylformamide with 1% acetic acid to give I-4. The resulting resin-bound aniline **I-4** is acylated with a commercially available or synthetically accessible, suitably substituted aryl or heteroaryl carboxylic acid **I-5**, for example 4-phenoxybenzoic acid, using, for example, N-bromo succinimide and triphenylphosphine in dichloromethane, or in dichloromethane in combination with dimethylformamide, in the presence of an organic base such as pyridine to afford **I-6**. For example, **1-4** is treated with a ten-fold excess of an equimolar mixture of a 3-aryl- or heteroaryl carboxylic acid, triphenylphosphine and N-bromosuccinimide, in a suitable solvent, such as dichloromethane, after which a ten-fold excess of a suitable base, such as pyridine, is added, and the mixture is gently agitated for a suitable time, for example, forty-eight hours, to afford the resin-bound amide **1-6**. Optionally, dimethylformamide may be added to the resulting mixture to increase the solubility of the 3-aryl- or heteroaryl carboxylic acid. Treatment of **I-6** with a mixture of a strong organic acid and organic solvent, such as trifluoroacetic

acid:dichloromethane:water (50:48:2), resulted in cleavage of the desired compound from the polymer support and afforded carboxanilide I-7, a compound of formula I.

Scheme I:




a) $Cl(CH_2)_2NR^3R^4$, $K_2CO_3$, $CH_3COCH_3$; (b) $H_2$, 5% Pd/C, MeOH; (c) Merrifield resin bound aldehyde (3); $NaBH(OAc)_3$, 1% HOAc, DMF; (d) aryl/heteroaryl carboxylic acid, NBS, $Ph_3P$, pyridine; (e) TFA, $CH_2Cl_2$, $H_2O$.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In the Examples, mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated.

## EXAMPLES

### Preparation 1

Preparation of 4-(Methylphenylamino)benzoic acid

A solution of ethyl 4-(methylphenylamino)benzoate (2.65 g, 10 mmol) (*Tetrahedron Lett.* **1997**, 38, 6359-6362) in tetrahydrofuran (50 mL), ethanol (25 mL), and water (5 mL) was treated with 1 N sodium hydroxide (84 mL) and heated to 50°C for 20 h. The mixture was reduced in volume *in vacuo*, diluted with water, and extracted three times with ethyl acetate. The aqueous phase was acidified with acetic acid to pH~6 and the white solid which precipitated was isolated by filtration, washed with water, and dried to give the title compound (1.95 g). MS (ES) m/e 227.8 $(M+H)^+$.

**Preparation 2**

Preparation of 1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'-piperidin]-5-amine

a) 5- and 7-nitrospiro[benzofuran-3(2H),4'-piperidine]

A solution of 1'-methyl-5- and 7-nitrospiro[benzofuran-3(2H),4'-piperidine] (WO 96/11934) (3 g, 12 mmol) and diisopropylethylamine (2.5 g, 19 mmol) in 1,2-dichloroethane (80 mL) was treated with 1-chloroethyl chloroformate (2.3 g, 16 mmol) at RT, stirred for 1 h, and heated to reflux for 20 min. The mixture was cooled, concentrated *in vacuo*, and the residue was dissolved in methanol and heated to reflux for 2 h, concentrated *in vacuo*, and the residue was partitioned between dichloromethane (250 mL) and 5% sodium bicarbonate (50 mL). The organic phase was washed with 5% sodium bicarbonate (50 mL) and the combined aqueous phase was extracted with dichloromethane (2 X 50 mL). The combined organic phase was dried ($Na_2SO_4$) and concentrated to afford the title compound (2. 65 g).

b) 1'-(tert-butoxycarbonyl)-5-nitrospiro[benzofuran-3(2H),4'-piperidine]

A solution of the compound of Preparation 2(a)(2.65 g, 1.13 mmol) in tetrahydrofuran (300 mL) was treated with di-tert-butyl dicarbonate (2.6 g, 12 mmol) and stirred at RT for 16 h. The mixture was concentrated *in vacuo* and the residue was crystallized from methanol to afford the title compound (2.1 g).

c) 5-nitrospiro[benzofuran-3(2H),4'-piperidine]

A solution of the compound of Preparation 2(b)(2.1 g, 6.3 mmol) in dichloromethane (50 mL) and trifluoroacetic acid (10 mL) was kept at RT for 5 h, concentrated *in vacuo*, and the residue was partitioned between dichloromethane (300 mL) and 5% sodium bicarbonate. The organic phase was washed with 5% sodium bicarbonate and the combined aqueous washes were extracted with dichloromethane. The combined organic phase was dried ($Na_2SO_4$) and concentrated *in vacuo* to give the title compound (1.45 g). MS(ES) m/e 235.1 $[+H]^+$.

d) 1'-(1-methylethyl)-5-nitrospiro[benzofuran-3(2H),4'-piperidine]

A mixture of the compound of Preparation 2(c) (1.45 g, 6.2 mmol), powdered potassium carbonate (0.86 g, 6.2 mmol) and dimethylformamide (50 mL)

containing 2-iodopropane (1.1 g, 6.4 mmol) was stirred and heated to 50°C for 4 h, treated with 2-iodopropane (0.17 g, 1 mmol) at 50°C for 90 min, and treated with 2-iodopropane (0.1 g, 1 mmol) at 50°C for 2 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (200 mL) and water (20 mL). The organic phase was washed, dried ($MgSO_4$), concentrated *in vacuo*, and the residue was chromatographed (silica gel, 5% methanol:dichloromethane) to give the title compound (0.85 g).

e) 1'-(1-methylethyl)spiro[benzofuran-3(2H),4'-piperidin]-5-amine

A solution of the compound of Preparation 2(d) (0.78 g, 2.8 mmol) in methanol (250 mL) containing 10% palladium-on-carbon (0.375 g) was shaken in a hydrogen atmosphere (40 psi) for 40 min, filtered, and concentrated *in vacuo* to afford the title compound (0.6 g).

**Preparation 3**

Preparation of 7-Amino-3,4-dihydro-N,N-bis(1-methylethyl)-1(2H)-quinolineethanamine

a) 3,4-dihydro-N,N-bis(1-methylethyl)-7-nitro-1(2H)-quinolineethanamine

Sodium carbonate (2.9 g, 27 mmol) was added to a mixture of 7-nitro-1,2,3,4-tetrahydroquinoline (1.2 g, 6.7 mmol) (United States Patent 5696133), 2-(diisopropylamino)ethyl chloride hydrochloride (4.0 g, 20 mmol), and ethanol (25 mL). The mixture was heated at reflux for 3 h, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography (silica gel, dichloromethane followed by 5% methanol:dichloromethane) to afford 1.4 g (68%) of the title compound as a yellow oil. MS(ES) m/e 306.1 $[M+H]^+$.

b) 7-amino-3,4-dihydro-N,N-bis(1-methylethyl)-1(2H)-quinolineethanamine

A mixture of the compound of Preparation 3(a) and 5% palladium-on-carbon in ethanol was hydrogenated at 50 psi. The mixture was filtered and concentrated *in vacuo* to afford the title compound.

**Preparation 4**

Preparation of 2-(Phenylmethyl)-4-thiazolecarboxylic Acid

A solution of benzeneethanethioamide (1.0 g, 6.6 mmol) in dioxane (25 mL) was treated with bromopyruvic acid (1.1 g, 6.6 mmol) and heated to 90°C for 4 h. The mixture was diluted with water and the tan crystals which formed were collected by filtration to afford the title compound.

**Example 1**

Preparation of N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide

a) 3-[2–(diethylamino)ethoxy]-4-methoxyaniline/[4-formyl-3,5-(dimethoxy)phenoxy]-Merrifield resin adduct

A mixture of [4-formyl-3,5-(dimethoxy)phenoxy]-Merrifield resin (Boojamra et al., *J. Org. Chem.* **1995**, 60, 5742-3), 3-[2-(diethylamino)ethoxy]-4-methoxyaniline (WO 95/15954), and sodium triacetoxyborohydride in dimethylformamide containing 1% acetic acid was shaken to afford the title adduct.

b) N-[3-[2–(diethylamino)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide/[4-formyl-3,5-(dimethoxy)phenoxy]-Merrifield resin adduct

The resin of Example 1(a) was placed in an Irori MicroKan and treated with a ten-fold molar excess of an equimolar mixture of 4-chlorocinnamic acid, N-bromosuccinimide, and triphenylphosphine in dichloromethane, followed by addition of a ten-fold excess of pyridine. The mixture was gently agitated for 48 h after which the resin was washed three-times, sequentially with dimethylformamide, dichloromethane, and methanol to afford the title adduct.

c) N-[3-[2–(diethylamino)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide

The resin of Example 1(b) was stirred in a mixture of trifluoroacetic acid:dichloromethane:water (50:48:2), filtered, and the filtrate concentrated *in vacuo* to afford the title compound. MS (ES) m/e 435.0 $(M+H)^+$.

**Examples 2-30**

Following the procedure of Example 1(a)-(c), except using 4-[(2-diisopropylamino)ethoxy]aniline (WO 99/01127), 4-[2-(diethylamino)ethoxy]aniline (*J. Med. Chem.* **1995**, 38, 1657-65), 3-[(2-diisopropylamino)ethoxy]aniline (WO 99/01127), 3-[(2-diisopropylamino)ethoxy]-4-methoxyaniline (WO 95/15954), 3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyaniline (WO 99/01127), and 3-[(3-diisopropylamino)propyl]-4-methoxyaniline (WO 99/01127) in addition to 3-[2-(diethylamino)ethoxy]-4-methoxyaniline, and except using 3-phenoxybenzoic acid, 4-(phenylmethyl)benzoic acid, 4-benzoylbenzoic acid, 4-[(4-chlorophenyl)sulfonyl]benzoic acid, 5-butylamino-4-phenoxy-3-(sulfamoyl)benzoic acid, 4-[(4-chlorophenyl)oxy]-3-nitrobenzoic acid, 2-[(4-carboxyphenyl)amino]quinoxaline, and 4-[(4-methylphenyl)sulfonyl]-3-nitrobenzoic acid in addition to 4-phenoxybenzoic acid, gave the title compounds:

N-[4-[2-[bis(1-methylethyl)amino]ethoxy]phenyl]]-4-phenoxybenzamide: MS (ES) m/e 433.2 $(M+H)^+$;

N-[4-[2-(diethylamino)ethoxy]phenyl]-4-phenoxybenzamide: MS (ES) m/e 405.2 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]phenyl]-4-phenoxybenzamide: MS (ES) m/e 433.2 $(M+H)^+$;

N-[3-[2-(diethylamino)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide: MS (ES) m/e 435.0 $(M+H)^+$;

N-[4-[2-[bis(1-methylethyl)amino]ethoxy]phenyl]-3-phenoxybenzamide: MS (ES) m/e 433.2 $(M+H)^+$;

N-[4-[2-[bis(1-methylethyl)amino]ethoxy]phenyl]-4-(phenylmethyl)benzamide: MS (ES) m/e 431.2 $(M+H)^+$;

N-[2-[2-(diethylamino)ethoxy]phenyl]-4-(phenylmethyl)benzamide: MS (ES) m/e 403.0 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-phenoxybenzamide: MS (ES) m/e 460.9 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide: MS (ES) m/e 502.9 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide: MS (ES) m/e 503.3 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-benzoylbenzamide: MS (ES) m/e 473.3 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide: MS (ES) m/e 515.3 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(phenylmethyl)benzamide: MS (ES) m/e 459.3 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide: MS (ES) m/e 501.3 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide: MS (ES) m/e 545.2 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide: MS (ES) m/e 543.2 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide: MS (ES) m/e 585.2 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide: MS (ES) m/e 613.3 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide: MS (ES) m/e 611.3 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide: MS (ES) m/e 653.3 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide: MS (ES) m/e 542.2 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide: MS (ES) m/e 540.2 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide: MS (ES) m/e 582.2 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide: MS (ES) m/e 514.4 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide: MS (ES) m/e 512.4 $(M+H)^+$;

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide: MS (ES) m/e 554.2 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide: MS (ES) m/e 570.2 $(M+H)^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide: MS (ES) m/e 568.3 $(M+H)^+$; and

N-[3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide: MS (ES) m/e 610.3 $(M+H)^+$.

**Example 31**

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide 3-Phenoxybenzoyl chloride, prepared from 3-phenoxybenzoic acid (0.11 g, 0.5 mmol) and thionyl chloride ( 5 mL) heated to reflux for 30 min, concentrated *in vacuo* and concentrated *in vacuo* from dichloromethane, was dissolved in dichloromethane (5 mL) and treated with 3-[(2-diisopropylamino)ethoxy]-4-methoxyaniline (0.14 g, 0.5 mmol) and diisopropylethylamine (0.07 g, 0.5 mmol). The mixture was stirred at RT for 16 h, and washed twice with 5% sodium carbonate and with water. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford a residue that was chromatographed (silica gel, 1:1 ethyl acetate:hexane) to give the title compound (0.12 g). MS (ES) m/e 463.2 $(M+H)^+$.

**Example 32-35**

Following the procedure of Example 31 except substituting 4-phenoxybenzoic acid, 4-(phenylmethyl)benzoic acid, 4-(phenylthio)benzoic acid, and 4-(phenylsulfonyl)benzoic acid (*Chim. Ther.* **1973**, 8, 340-1) for 3-phenoxybenzoic acid, gave the title compounds:

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide: MS (ES) m/e 463.0 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide: MS (ES) m/e 460.9 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylthio)benzamide: MS (ES) m/e 478.9 $(M+H)^+$; and

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfonyl)benzamide: MS (ES) m/e 510.7 $(M+H)^+$.

**Example 36**

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(3-hydroxyphenoxy)benzamide A solution of 4-(3-hydroxyphenoxy)benzoic acid (0.23 g, 1 mmol), 3-[(2-diisopropylamino)ethoxy]-4-methoxyaniline (0.27 g, 1 mmol), and BOP reagent (0.44 g, 1 mmol) in acetonitrile (20 mL) was treated with triethylamine (0.2 g, 2 mmol) and stirred at RT for 16 h. The mixture was diluted with dichloromethane and filtered. The filtrate was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to afford a residue that was purified by HPLC (ODS-A, 20 X 50 mm, A:acetonitrile B:water-0.1% trifluoroacetic acid, 10-90% during 10 min, UV detection at 254 nm) to afford the title compound. MS (ES) m/e 478.8 $(M+H)^+$.

## Examples 37-43

Following the procedure of Example 36, except substituting 4-[(4-chlorophenyl)sulfinyl]-3-nitrobenzoic acid, 4-[(2,4-dichlorophenyl)sulfinyl]-3-nitrobenzoic acid, 4-benzoylbenzoic acid, 3-benzoylbenzoic acid, the compound of Preparation 1, 4-(phenylamino)benzoic acid, and 4-(phenylsulfinyl)benzoic acid (*Synthesis* **1990**, 847-9) for 4-(3-hydroxyphenoxy)benzoic acid, afforded the title compounds:

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfinyl]-3-nitrobenzamide: MS (ES) m/e 573.7 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(2,4-dichlorophenyl)sulfinyl]-3-nitrobenzamide: MS (ES) m/e 607.7 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide: MS (ES) m/e 475.3 $(M+H)^+$;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-benzoylbenzamide: MS (ES) m/e 474.9 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(methylphenylamino)benzamide: MS (ES) m/e 475.9 $(M+H)^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylamino)benzamide: MS (ES) m/e 462.0 $(M+H)^+$; and

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfinyl)benzamide: MS (ES) m/e 494.7 $(M+H)^+$.

## Example 44

Preparation of N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-phenoxybenzamide Following the procedure of Example 36, except substituting 4-phenoxybenzoic acid for 4-(3-hydroxyphenoxy)benzoic acid and 3-[(3-diisopropylamino)propyl]-4-methoxyaniline for 3-[(2-diisopropylamino)ethoxy]-4-methoxyaniline, afforded the title compound. MS (ES) m/e 461.3 $(M+H)^+$.

## Example 45

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(hydroxyimino)phenylmethyl]benzamide A solution of the compound of Example 39 (0.24 g, 0.5 mmol), hydroxylamine hydrochloride (0.17 g), and triethylamine (0.24 mL) in ethanol (10 mL) was heated to reflux for 20 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and water to give the title compound. MS (ES) m/e 490.0 $(M+H)^+$.

**Example 46**

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(hydroxyphenylmethyl)benzamide A mixture of the compound of Example 39 (0.24 g, 0.5 mmol), ethanol (21 mL), water (7 mL), methanol (5 mL), and dichloromethane (5 mL) was treated with sodium borohydride (0.13 g, 3.5 mmol) and stirred at RT for 2 h. The mixture was diluted with water, reduced in volume *in vacuo*, and extracted three times with dichloromethane. The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (40 mg). MS (ES) m/e 477.2 $(M+H)^+$.

**Example 47**

Preparation of N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-benzoylbenzamide trifluoroacetate A solution of 4-benzoylbenzoic acid (55 mg, 0.254 mmol), the compound of Preparation 2(e) (60 mg, 0.24 mmol), and BOP reagent (108 mg, 0.24 mmol) in acetonitrile (5 mL) was treated with triethylamine (50 mg, 0.5 mmol) and stirred at RT for 16 h. The mixture was quenched with brine and extracted with ethyl acetate. The organic extract was washed with 5% sodium carbonate and with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by HPLC (ODS-A, 20 X 50 mm, A:acetonitrile B:water-0.1% trifluoroacetic acid, 10-90% during 10 min, UV detection at 254 nm) to give the title compound. MS (ES) m/e 455.1 $(M+H)^+$.

**Examples 48-49**

Preparation of N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide and N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide

Following the procedure of Example 47, except substituting 4-phenoxybenzoic acid and 4-(phenylthio)benzoic acid for 4-benzoylbenzoic acid, gave the title compounds:

N-[1'-(1-methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide: MS (ES) m/e 443.1 $(M+H)^+$; and

N-[1'-(1-methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide: MS (ES) m/e 459.1 $(M+H)^+$.

**Example 50**

Preparation of N-[1-[2-[Bis(1-methylethyl)amino]ethyl]-1,2,3,4-tetrahydroquinol-7-yl]-4-phenoxybenzamide Following the procedure of Example 31, except substituting 4-phenoxybenzoic acid for 3-phenoxybenzoic acid and substituting the compound of Preparation 3(b) for 3-[(2-diisopropylamino)ethoxy]-4-methoxyaniline, gave the title compound. MS (ES) m/e 472.2 $(M+H)^+$.

**Example 51**

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide Methiodide The compound of Example 32 (93 mg, 0.2 mmol) in methanol (3 mL) was treated with iodomethane (8 mL), maintained at RT for 4 d, concentrated *in vacuo*, and the residue was triturated with ethyl acetate and then with1:1 ethyl acetate:ether. The residue was stirred with 1:1 ethyl acetate:ether for several hours and filtered to afford the title compound. MS (ES) m/e 477 $(M+H)^+$.

**Example 52**

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2-(phenylmethyl)thiazole-4-carboxamide hydrochloride

Following the procedure of Example 31, except substituting the compound of Preparation 4 for 3-phenoxybenzoic acid, afforded the title compound. MS (ES) m/e 468.0 $(M+H)^+$.

**Biological Data:**

CCR5 Receptor Binding Assay CHO cell membranes ($0.25 \times 10^6$ cell equivalents) derived from CHO cells stably transfected with CCR5 were incubated with 0.3 $^{125}$I-RANTES in a 96 well plate for 45 min at room temperature (final reaction volume 200 ul). The reaction was terminated by filtration and the filters (GF/C) were washed twelve times with a solution of phosphate buffered saline containing 0.1 % bovine serum albumin and 0.05 % $NaN_3$. The radioactivity bound to filters was measured by liquid scintillation spectrometry. Non-specific binding was determined in the presence of unlabelled RANTES (10 or 30 nM) and averages 30-50% of total binding.

CCR5 Receptor Functional Assay

The cellular functional assay used to assess antagonist activity of compounds was RANTES-induced $Ca^{2+}$ mobilization in RBL 2H3 cells stably expressing the hCCR5 receptor (RBL 2H3 hCCR5). Agonist activity is determined by $Ca^{2+}$ mobilization in the same cells which is inhibitable by a selective CCR5 antagonist. Cells were grown to 80-100% confluency in T-150 flasks and washed with phosphate-buffered saline. Cells were lifted from the flasks by treating with 3 mL of 1 mM EDTA for 3 min at room temperature and diluting to $2 \times 10^6$ cells/mL with Krebs Ringer Henseleit buffer (KRH; 118 mM NaCl, 4.6 mM KCl, 25 mM $NaHCO_3$, 1 mM $KH_2PO_4$ and 11 mM glucose) containing 5

mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% BSA and centrifuged at 200g for 3 min. Cells were resuspended at 2 X $10^6$ cells/mL in the same buffer with 2 μM Fura-2AM, and incubated for 35 min at 37° C. Cells were centrifuged at 200 x g for 3 min and resuspended in the same buffer without Fura-2AM, then incubated for 15 min at 37° C to complete the hydrolysis of intracellular Fura-2AM, and then centrifuged as before. Cells ($10^6$ cells/mL) were resuspended in cold KRH with 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% gelatin and maintained on ice until assayed. For antagonist studies, aliquots (2 mL) of cells were prewarmed at 37° C for 5 min in 3 mL plastic cuvettes and fluorescence measured in a fluorometer (Johnson Foundation Biomedical Group, Philadelphia, PA, USA) with magnetic stirring and temperature maintained at 37° C. Excitation was set at 340 nm and emission set at 510 nm. Various concentrations of antagonists or vehicle were added and fluorescence monitored for ~15 sec to ensure that there was no change in baseline fluorescence, followed by the addition of 33 nM RANTES. Maximal $Ca^{2+}$ attained after 33 nM RANTES stimulation was calculated as described by Grynkiewicz *et al.*, (1985). The percent of maximal RANTES-induced $Ca^{2+}$ was determined for each concentration of antagonist and the $IC_{50}$, defined as the concentration of test compound that inhibits 50% of the maximal 33 nM RANTES response, obtained from the concentration-response curves (5-7 concentrations of antagonists).

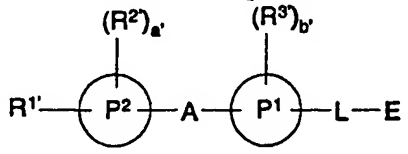
The compounds of this invention show CCR5 receptor modulator activity having $IC_{50}$ values in the range of 0.0001 to 100 μM. The full structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of this invention are modulators of the CCR5 receptor and which bind thereto with an $IC_{50}$ value in the range of 0.0001 to 100 μM.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration it is believed that one skilled in the art can, given the preceding description, utilize the present invention to its fullest extent. Therefore any examples are to be construed as merely illustrative and not a limitation on the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A method of treating a CCR5-mediated disease state in mammals which comprises administering to a mammal in need of such treatment, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:




Formula I

wherein:

the basic nitrogen in moiety E may be optionally quaternized with $C_{1-6}$alkyl or is optionally present as the N-oxide;

$P^1$ and $P^2$ are independently phenyl, fused bicyclic aryl, a monocyclic heterocyclic ring of 5- to 7-members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, or a fused bicyclic heterocyclic ring of 8 to 11-members containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

A is $C(R^{4'})_2$, $CR^{4'}(OR^{5'})$, CO, $C{=}NOR^{6'}$, $NR^{7'}$, oxygen, or $S(O)_{c'}$;

L is a group of formula $-C(=V)-DR^{8'}-$, $-DR^{9'}-C(=V)-$, $-CH_2NH-$, or $-NHCH_2-$;

V is oxygen or sulfur;

D is nitrogen, carbon, or a CH group,

$R^{1'}$ and $R^{2'}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkenyl, aryl, $(CH_2)_{d'}NR^{10'}R^{11'}$, $(CH_2)_{d'}NR^{10'}COR^{12'}$, $(CH_2)_{d'}NR^{10'}CO_2R^{13'}$, $(CH_2)_{d'}NR^{10'}SO_2R^{14'}$, $(CH_2)_{d'}CONR^{15'}R^{16'}$, hydroxy$C_{1-6}$alkyl, $C_{1-4}$alkoxyalkyl (optionally substituted by a $C_{1-4}$alkoxy or hydroxy group), $(CH_2)_{d'}CO_2C_{1-6}$alkyl, $(CH_2)_{e'}OC(O)R^{17'}$, $CR^{18'}{=}NOR^{19'}$, $CNR^{20'}{=}NOR^{19'}$, $COR^{21'}$, $CONR^{15'}R^{16'}$, $CONR^{15'}(CH_2)_{f'}OC_{1-4}$alkyl, $CONR^{15'}(CH_2)_{d'}CO_2R^{22'}$, $CONHNR^{23'}R^{24'}$, $CONR^{15'}SO_2R^{25'}$, $CO_2R^{26'}$, cyano, trifluoromethyl, $NR^{10'}R^{11'}$, $NR^{10'}COR^{12'}$, $NR^{27'}CO(CH_2)_{d'}NR^{27'}R^{28'}$, $NR^{27'}CONR^{27'}R^{28'}$, $NR^{10'}CO_2R^{13'}$, $NR^{10'}SO_2R^{14'}$, $N{=}CNR^{27'}NR^{27'}R^{28'}$, nitro, hydroxy, $C_{1-6}$alkoxy, hydroxy$C_{1-6}$alkoxy, $C_{1-6}$alkoxy$C_{1-6}$alkoxy, $OC(O)NR^{29'}R^{30'}$, $SR^{31'}$, $SOR^{32'}$, $SO_2R^{32'}$, $SO_2NR^{33'}R^{34'}$, halogen, $C_{1-6}$alkanoyl, $CO_2(CH_2)_{d'}OR^{35'}$, or $R^{1'}$ is an optionally substituted 5 to 7-

membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;

$R^{3'}$ is hydrogen, $C_{1-6}$alkyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkenyl, hydroxy$C_{1-6}$alkyl, $C_{1-6}$alkyl$OC_{1-6}$alkyl, $CONR^{36'}R^{37'}$, $CO_2R^{38'}$, cyano, aryl, trifluoromethyl, $NR^{39'}R^{40'}$, nitro, hydroxy, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, acyloxy, or halogen;

$R^{4'}$, $R^{5'}$, $R^{6'}$, $R^{7'}$, $R^{18'}$, $R^{19'}$, $R^{20'}$, $R^{21'}$, $R^{22'}$, $R^{23'}$, $R^{24'}$, $R^{27'}$, $R^{28'}$, $R^{31'}$, $R^{35'}$, $R^{36'}$, $R^{37'}$, $R^{38'}$, $R^{39'}$, and $R^{40'}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{8'}$ is hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group;

$R^{9'}$ is hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group;

$R^{10'}$ and $R^{11'}$ are independently hydrogen or $C_{1-6}$alkyl, or $R^{10'}$ and $R^{11'}$ together with the nitrogen to which they are attached, forms a 5- to 6-membered heterocyclic ring, which may optionally be substituted by an oxo group, and, when there are six members, may optionally contain in the ring one oxygen or one sulfur atom;

$R^{12'}$ is hydrogen, $C_{1-6}$alkyl, or $C_{1-4}$alkoxyalkyl;

$R^{13'}$, $R^{25'}$, and $R^{32'}$ are independently $C_{1-6}$alkyl;

$R^{14'}$ is $C_{1-6}$alkyl or phenyl;

$R^{15'}$ and $R^{16'}$ are independently hydrogen or $C_{1-6}$alkyl, or $R^{15'}$ and $R^{16'}$ together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when there are 6 ring members, may optionally contain in the ring one oxygen or one sulfur atom;

$R^{17'}$ is $C^{1-4}$alkyl, optionally substituted by $C_{1-6}$alkoxy;

$R^{26'}$ is hydrogen or $C_{1-6}$alkyl optionally substituted with one or two substituents selected from $C_{1-6}$alkyl, $C_{1-6}$alkoxy, hydroxy, or $NR^{10'}R^{11'}$;

$R^{29'}$ and $R^{30'}$ are independently hydrogen or $C_{1-6}$alkyl, or $R^{29'}$ and $R^{30'}$ together with the nitrogen to which they are attached form a 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or sulfur atom;

$R^{33'}$ and $R^{34'}$ are independently hydrogen or $C_{1-6}$alkyl, or $R^{33'}$ and $R^{34'}$ together with the nitrogen to which they are attached form 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or one sulfur atom;

a' and b' are independently 1, 2, or 3;

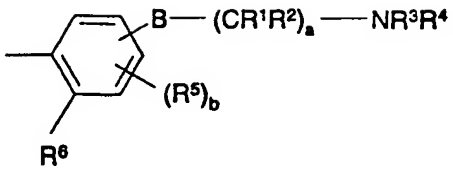
c' is 0, 1, or 2;

d' is 1, 2, 3, or 4;

e' is 0, 1, 2, or 3;

f' is 1, 2, or 3;

E represents (a):




(a);

in which

B is oxygen, $S(O)_c$, $CR^7=CR^8$, or $CR^7R^8$, or B is $NR^9$;

$R^1$ and $R^2$ are independently hydrogen or $C_{1-6}$alkyl; alternatively $B(CR^1R^2)_a$ is $OCR^1R^2CR^1(OH)CR^1R^2$ or $OCR^1R^2CR^1(OCOCH_3)CR^1R^2$;

$R^3$ and $R^4$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, hydroxy, $OCOR^{12}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{13}$, and $NHCO_2R^{14}$;

$R^5$ is hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{15}R^{16}$, $CO_2R^{17}$, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$ or halogen;

$R^6$ is hydrogen, $C_{1-6}$alkyl, aryl, trifluoromethyl, hydroxy, $C_{1-6}$alkoxy or halogen, or $R^6$ taken together with $R^{8'}$ forms a group D where D is $(CR^{22}R^{23})_e$ or D is $(CR^{22}R^{23})_f$-G where G is oxygen, sulfur or $CR^{22}=CR^{23}$, $CR^{22}=N$, $=CR^{22}O$, $=CR^{22}S$, or $=CR^{22}$-$NR^{23}$;

$R^7$, $R^8$, $R^{10}$, $R^{11}$, $R^{12}$, $R^{15}$, $R^{16}$, $R^{17}$, $R^{20}$, $R^{21}$, $R^{22}$, and $R^{23}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^9$ is hydrogen, $C_{1-6}$alkyl, or phenyl$C_{1-6}$alkyl;

$R^{13}$, $R^{14}$, $R^{18}$, and $R^{19}$ are independently $C_{1-6}$alkyl;

a is 1, 2, 3, or 4;

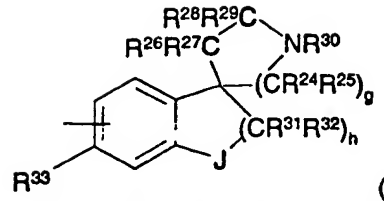
b is 1 or 2;

c and d are independently 0, 1 or 2;

e is 2, 3 or 4;

f is 0, 1, 2 or 3;

alternatively, E represents (b):




(b);

$R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{31}$, and $R^{32}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{30}$ is hydrogen, $C_{1-6}$alkyl, or $C_{3-7}$cycloalkyl;

$R^{33}$ is hydrogen, $C_{1-6}$alkyl, trifluoromethyl, hydroxy, or halogen, or $R^{33}$ and $R^{8'}$ together form a group -K- where K is $(CR^{34}R^{35})_i$ or K is $(CR^{34}R^{35})_j$ -M and M is oxygen, sulfur, $CR^{34}=CR^{35}$, $CR^{34}=N$, or N=N;

J is oxygen, $CR^{36}R^{37}$, or $NR^{38}$, or J is a group $S(O)_k$;

$R^{34}$, $R^{35}$, $R^{36}$, $R^{37}$, and $R^{38}$ are independently hydrogen or $C_{1-6}$alkyl;

g is 1, 2 or 3;

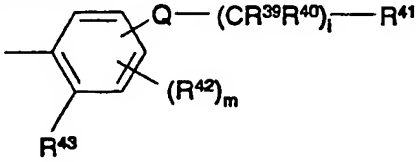
h is 1, 2 or 3;

i is 2, 3, or 4;

j is 0, 1, 2, or 3;

k is 0, 1 or 2;

alternatively, E represents (c):



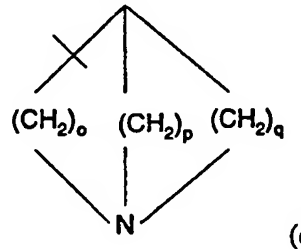

(c);

in which:

Q is oxygen, $S(O)_n$, $CR^{44}=CR^{45}$, $CR^{44}R^{45}$, or Q is $NR^{46}$;

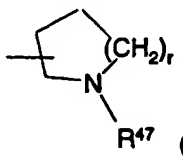
$R^{39}$ and $R^{40}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{41}$ is a group of formula (d):




(d)

or $R^{41}$ is a group of formula (e):




(e)

$R^{42}$ is hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{48}R^{49}$, $CO_2R^{50}$, trifluoromethyl, $NHCO_2R^{51}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_sR^{52}$, $SO_2NR^{53}R^{54}$, or halogen;

$R^{43}$ is hydrogen or $R^{43}$ together with $R^{8'}$ forms a group R where R is $CR^{55}=CR^{56}$, $CR^{55}=CR^{56}CR^{55}R^{56}$, or $(CR^{55}R^{56})t$;

$R^{44}$, $R^{45}$, $R^{46}$, $R^{48}$, $R^{49}$, $R^{50}$, $R^{53}$, $R^{54}$, $R^{55}$, and $R^{56}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{47}$ is hydrogen, $C_{1-6}$alkyl, or $C_{3-7}$ cycloalkyl;

$R^{51}$ and $R^{52}$ are independently $C_{1-6}$alkyl;

l is 0, 1, 2, or 3;

m is 1 or 2;

n is 0, 1, or 2

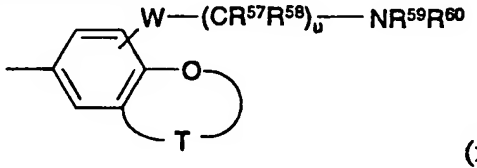
o, p, and q are independently integers having the value 1, 2, or 3;

r is 0,1, 2, or 3;

s is 0, 1, or 2;

t is 2 or 3;

alternatively, E represents (f):




(f);

$R^{57}$ and $R^{58}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{59}$ and $R^{60}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{61}R^{62}$, $NR^{61}R^{62}$, hydroxy, $OCOR^{63}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{64}$, and $NHCO_2R^{65}$;

T is $-(CR^{66}R^{67})_v-$ or $-O(CR^{66}R^{67})_w-$;

W is oxygen, $S(O)_x$, $NR^{68}$, or W is $CR^{69}=CR^{70}$ or $CR^{69}R^{70}$;

$R^{61}$, $R^{62}$, $R^{63}$, $R^{66}$, $R^{67}$ $R^{68}$, $R^{69}$, and $R^{70}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{64}$ and $R^{65}$ are independently $C_{1-6}$alkyl;

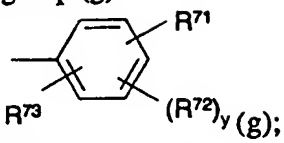
u is 1 to 4;

v is 2 or 3;

w is 1, 2, or 3;

x is 0, 1 or 2;

alternatively, E represents a group (g):



(g);

$R^{71}$ is an optionally substituted 5 to 7-membered saturated or partially saturated heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur or $R^{71}$ is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom and optionally a further heteroatom selected from oxygen, nitrogen or sulfur;

$R^{72}$ is hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{74}R^{75}$, $CO_2R^{76}$, trifluoromethyl, $NHCO_2R^{77}$, hydroxy, $C_{1-6}$alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, $OCF_3$, $S(O)_zR^{78}$, $SO_2NR^{79}R^{80}$, or halogen;

$R^{73}$ is hydrogen, $C_{1-6}$alkyl, hydroxy, $C_{1-6}$alkoxy or halogen, or $R^{73}$ and $R^{8'}$ taken together from a group -X- where X is $(CR^{81}R^{82})_{aa}$ or X is $(CR^{81}R^{82})_{ab}$-Y and Y is oxygen, sulfur or $CR^{81}=CR^{82}$;

$R^{74}$, $R^{75}$, $R^{76}$, $R^{79}$, $R^{80}$, $R^{81}$, and $R^{82}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{77}$ and $R^{78}$are independently $C_{1-6}$alkyl;

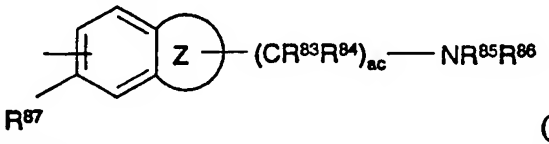
y is 1 or 2;

z is 0, 1, or 2;

aa is 2, 3 or 4;

ab is 0, 1, 2 or 3;

alternatively, E represents group (h):



(h);

$R^{83}$ and $R^{84}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{85}$ and $R^{86}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{88}R^{89}$, $NR^{90}R^{91}$, hydroxy, $OCOR^{92}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{93}$, and $NHCO_2R^{94}$;

$R^{87}$ is hydrogen or $C_{1-6}$alkyl, $C_{1-6}$alkoxy, or halogen, or $R^{87}$ together with $R^{8'}$ forms a group -AA- where AA is $(CR^{95}R^{96})_{ad}$ or AA is $(CR^{95}=CR^{96})_{ae}$-AB and AB is oxygen, sulfur, $CR^{95}=CR^{96}$, $CR^{95}=N$, $CR^{95}NR^{96}$ or N=N;

Z is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

$R^{88}$, $R^{89}$, $R^{90}$, $R^{91}$, $R^{92}$, $R^{95}$, and $R^{96}$ are independently hydrogen or $C_{1-6}$alkyl;

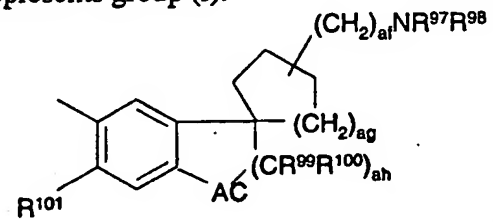
$R^{93}$ and $R^{94}$ are independently $C_{1-6}$alkyl;

ac is 0 to 4;

ad is 1, 2 or 3;

ae is 0, 1 or 2;

alternatively, E represents group (i):




(i);

$R^{97}$ and $R^{98}$ are independently hydrogen, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_{1-6}$alkyl, aryl, $CONR^{102}R^{103}$, $NR^{104}R^{105}$, hydroxy, $OCOR^{106}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{107}$, and $NHCO_2R^{108}$;

$R^{99}$ and $R^{100}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{101}$ is hydrogen or $C_{1-6}$alkyl or $R^{101}$ and $R^{8'}$ together form a group -AD- where AD is $(CR^{109}R^{110})$ai or AD is $(CR^{109}R^{110})_{aj}$-AE and AE is oxygen, sulfur or $CR^{109}=CR^{110}$;

AC is oxygen, $CR^{111}R^{112}$ or $NR^{113}$ or AC is a group $S(O)_{ak}$;

$R^{102}$, $R^{103}$, $R^{104}$, $R^{105}$, $R^{106}$, $R^{109}$, $R^{110}$, $R^{111}$, $R^{112}$, and $R^{113}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{107}$ and $R^{108}$ are independently $C_{1-6}$alkyl;

af is 0, 1, 2, 3, or 4;

ag is 1, 2, or 3;

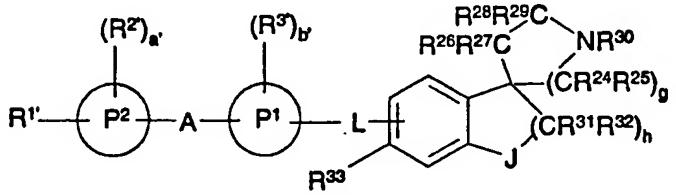
ah is 1, 2, 3 or 4;

ai is 2, 3 or 4;

aj is 0, 1, 2, or 3; and

ak is 0, 1 or 2.

2. The method of claim 1 wherein the compound of formula (I) is selected from a subgenus of formula (Ia) or a pharmaceutically acceptable salt thereof:



Formula (Ia)

wherein:
$R^{1'}$, $R^{2'}$, $R^{3'}$, $P^1$, $P^2$, A, a', b', L, $R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{30}$, $R^{31}$, $R^{32}$, $R^{33}$, J, g, and h are defined in claim 1.

3. The method as claimed in claim 1 wherein the compound is selected from:

N-[4-[2-(Dimethylamino)ethyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl)-4-phenoxybenzamide;

N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]]-4-phenoxybenzamide;

N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-3-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-(phenylmethyl)benzamide;

N-[2-[2-(Diethylamino)ethoxy]phenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2-(phenylmethyl)thiazole-4-carboxamide hydrochloride;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide Methiodide;

N-[1-[2-[Bis(1-methylethyl)amino]ethyl]-1,2,3,4-tetrahydroquinol-7-yl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(3-hydroxyphenoxy)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfinyl]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(2,4-dichlorophenyl)sulfinyl]-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-benzoylbenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(methylphenylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylthio)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfonyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfinyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(hydroxyimino)phenylmethyl]benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(hydroxyphenylmethyl)benzamide;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-benzoylbenzamide trifluoroacetate;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide; and

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide;

or a pharmaceutically acceptable salt thereof.

4. The method of claim 1 wherein the CCR5-mediated disease state is selected from COPD, asthma and atopic disorders, rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic disease, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV.

5. A compound of formula (I) selected from:

N-[4-[2-(Dimethylamino)ethyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl)-4-phenoxybenzamide;

N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]]-4-phenoxybenzamide;

N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(Diethylamino)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-3-phenoxybenzamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-(phenylmethyl)benzamide;

N-[2-[2-(Diethylamino)ethoxy]phenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2-(phenylmethyl)thiazole-4-carboxamide hydrochloride;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide Methiodide;

N-[1-[2-[Bis(1-methylethyl)amino]ethyl]-1,2,3,4-tetrahydroquinol-7-yl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(3-hydroxyphenoxy)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfinyl]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(2,4-dichlorophenyl)sulfinyl]-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-3-phenoxybenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-phenoxybenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-benzoylbenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(phenylmethyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-chlorophenyl)sulfonyl]benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-5-butylamino-4-phenoxy-3-(sulfamoyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(4-chlorophenoxy)-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-(2-quinoxalinylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[2-(2,2,6,6-Tetramethyl-1-piperidinyl)ethoxy]-4-methoxyphenyl]-4-[(4-methylphenyl)sulfonyl]-3-nitrobenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-benzoylbenzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(methylphenylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylamino)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylthio)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfonyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(phenylsulfinyl)benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-[(hydroxyimino)phenylmethyl]benzamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(hydroxyphenylmethyl)benzamide;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-benzoylbenzamide trifluoroacetate;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-phenoxybenzamide; and

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'5-piperidin]-5-yl]-4-(phenylthio)benzamide.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US99/17121

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 31/165; C07D 235/56
US CL 514/618, 620, 621, 622; 564/168, 169, 171
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. 514/618, 620, 621, 622, 564/168, 169, 171

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN/CAS, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim |
|---|---|---|
| A | US 4,263,039 A (NOGUCHI et al.) 21 April 1981 (21.04.81), see entire document. | 1-5 |

☐ Further documents are listed in the continuation of Box C ☐ See patent family annex

| | | | |
|---|---|---|---|
| * | Special categories of cited documents | "T" | later document published after the international filing date or prior date and not in conflict with the application but cited to understan the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance, the claimed invention cannot considered novel or cannot be considered to involve an inventive st when the document is taken alone |
| "E" | earlier document published on or after the international filing date | "Y" | document of particular relevance, the claimed invention cannot considered to involve an inventive step when the document combined with one or more other such documents, such combinatio being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

| | |
|---|---|
| Date of the actual completion of the international search<br>10 JANUARY 2000 | Date of mailing of the international search report<br>20 JAN 2000 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>RICHARD L. RAYMOND<br>Telephone No. (703) 308-0196 |

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